SLEEP, CIRCADIAN RHYTHMS, AND AGING: NEW AVENUES FOR IMPROVING BRAIN HEALTH, PHYSICAL HEALTH AND FUNCTIONING

8TH ANNUAL BEDSIDE TO BENCH CONFERENCE
TUESDAY, OCTOBER 6, 2015

SLEEP IN INSTITUTIONALIZED ELDERLY

Kathy Richards, PhD, RN, FAAN
George Mason University
CURRENT FUNDING:
NATIONAL INSTITUTES OF HEALTH
PHILLIPS RESPIRONICS FOR CPAP UNITS FOR CLINICAL TRIAL

OTHER FINANCIAL RELATIONSHIPS:
NONE

CONFLICTS OF INTEREST:
NONE
SIGNIFICANCE

PORTRAIT OF MARGUERITE SLEEPING
BY HENRY MATISSE
SLEEP DISTURBANCE AND DEMENTIA ARE PREVALENT AND SEVERE

- 75% if institutionalized older adults have dementia
- 25-50% of institutionalized older adults have sleep disturbance

Characteristics of sleep
- Difficulty falling asleep
- Increased nighttime awakenings
- Decreased slow-wave and REM sleep
- Increased daytime napping
- Rest-activity rhythm fragmentation with high levels of activity during the night
- Increased agitation in the late afternoon, evening, and night “Sundowning”
CONSEQUENCES OF SLEEP DISTURBANCE

- Increased stress and reduced quality of life for patients
- Burdened caregivers
- Institutionalization
- May Accelerate Cognitive decline
CAUSES FOR SLEEP DISTURBANCE

INSTITUTIONAL ENVIRONMENT

INSUFFICIENT LIGHT, LACK OF MEANINGFUL SOCIAL ACTIVITY, PHYSICAL INACTIVITY, EXCESSIVE NAPPING, EXCESSIVE TIME IN BED, FREQUENT AWAKENINGS BY STAFF FOR CARE, NOISE FROM STAFF AND OTHER RESIDENTS

SLEEP DISORDERS

OBSTRUCTIVE SLEEP APNEA
RESTLESS LEGS SYNDROME
STATE-OF-THE-ART KNOWLEDGE
SEARCH STRATEGY


Clinical Trials
Sleep in Dementia (209), Sleep in Nursing Home (128)
74 ARTICLES
½ INVOLVED LIGHT, PHYSICAL ACTIVITY, AND/OR
MELATONIN

Sleep by Henry Matisse
INSUFFICIENT LIGHT

- Light is the most powerful synchronizer
- Aging results in loss of robustness of circadian rhythms
  - Reduction in suprachiasmatic nuclei numbers and activity
  - Reduced sensitivity of the retina to light
  - Yellowing of the lens
  - Smaller pupil diameter
- Light exposure in nursing homes has been shown to be extremely low and vary little between day and night
BRIGHT LIGHT THERAPY

- 20 trials on the effect of bright light to strengthen the circadian rhythm and improve sleep in nursing homes and long-stay wards
- Bright white light, varying intensity
- 2009 Cochrane meta-analysis in nursing home residents concluded insufficient evidence as too few studies of high quality
- 2011 review concluded bright light therapy applied at an intensity of >2500 lux in Alzheimer’s Disease patients showed a trend to improve nighttime sleep and reduce daytime sleepiness

- Ploeg ES, O’Connor DW. Methodological challenges in studies of bright light therapy to treat sleep disorders in nursing home residents with dementia. Psychiatry and Clinical Neurosciences 2014;6;777-784.
EFFECT OF MELATONIN ON SLEEP AND COGNITION IN DEMENTIA

- 7 studies (N = 520)
- Dosage 2.5 mg – 10 mg
- Total sleep time significantly improved (mean 24.36 minutes)
- Sleep efficiency marginal (mean difference 1.78, p .07)
- No significant effect on cognition
- Effect greater if study duration more than 4 weeks

Effect of Bright Light and Melatonin

Objective: to test long-term use of 2 major synchronizers of circadian timing for cognitive and non-cognitive outcomes

Interventions: random assignment by facility to bright light or control light, and by participant to melatonin or placebo

Findings:
• melatonin shortened sleep latency (8.2 min) and increased sleep duration (27 min), but worsened mood scores
• combination treatment (melatonin + light) increased sleep efficiency and improved nocturnal restlessness, and attenuated some adverse effects of melatonin

Conclusion: melatonin is only recommended in combination with bright light therapy

Riemersma-Van Der Lek RF, Swaab DF, Twisk J, et al. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. JAMA 2008;299:2642-2655.
INSUFFICIENT SOCIAL AND PHYSICAL ACTIVITY

- Both daytime social and physical activity are time cues for circadian rhythms of sleep and wake.

- Other ways social and physical activity may influence sleep:
  - Improved mood and cognition may mediate the effect of stimulating social activities on sleep.
  - Improved function and reduced apnea-hypopnea index may mediate the effect of exercise on sleep.

Research: Social Activity and Excessive Daytime Napping

Daytime Minutes Slept (n = 139)

$p = .001$
Research: Social Activity and Excessive Daytime Napping

Day/Night Sleep Ratio (n = 139)

\[ p = .04 \]
RESULTS: EFFECT OF SOCIAL ACTIVITIES AND EXERCISE ON SLEEP IN DEMENTIA

Significant Pairwise comparison:
Mean difference (Combined Group – Control) = 35.23; SE = 13.72; p = .011
RESULTS: EFFECT OF SOCIAL ACTIVITIES AND EXERCISE ON SLEEP IN DEMENTIA

Adjusted Means for Post-intervention Comparison of Sleep Efficiency (%)

- Control: 68.5
- Individualized Social Activity (ISA): 69.7
- Physical Resistance Training (PRT): 71.1
- Combined ISA & PRT: 73.3

Significant Pairwise comparison:
Mean difference (Combined Group – Control) = 4.77; SE = 2.015; p = .019
RESULTS: EFFECT OF SOCIAL ACTIVITIES AND EXERCISE ON SLEEP IN DEMENTIA

Adjusted Means for Post-intervention Comparison of NREM sleep (minutes)

Significant Pairwise comparisons:
Mean difference (Combined Group – Control) = 32.64; SE = 12.19; \( p = .008 \)
(Combined Group – ISA) = 31.52; SE = 11.93; \( p = .009 \)
(Combined Group – PRT) = 28.11; SE = 11.69; \( p = .017 \)
STRENGTH TRAINING, WALKING, AND SOCIAL ACTIVITY IMPROVE SLEEP IN NURSING HOME AND ASSISTED LIVING RESIDENTS: RANDOMIZED CONTROLLED TRIAL

Table 3. Analysis of Covariance (ANCOVA), Pairwise Comparisons, and Effect Sizes on Polysomnography Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Exercise</th>
<th>Social Activity</th>
<th>Combined Exercise and Social Activity</th>
<th>Control</th>
<th>ANCOVA Between Treatment</th>
<th>ANCOVA Covariate</th>
<th>ANCOVA Interaction</th>
<th>SPSS Pairwise Comparisons</th>
<th>ES (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total nocturnal sleep time, minutes</td>
<td>340.7 (58.5)</td>
<td>342.1 (55.8)</td>
<td>364.2 (46.7)</td>
<td>328.9 (81.4)</td>
<td>6.17</td>
<td>.001*</td>
<td>.32</td>
<td>70.58 &lt; .001</td>
<td>4.45</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>71.1 (7.5)</td>
<td>69.7 (8.4)</td>
<td>73.3 (9.0)</td>
<td>68.5 (11.7)</td>
<td>5.54</td>
<td>.001*</td>
<td>.30</td>
<td>92.79 &lt; .001</td>
<td>4.75</td>
</tr>
<tr>
<td>Non-rapid eye movement sleep, minutes</td>
<td>298.3 (50.1)</td>
<td>294.9 (51.6)</td>
<td>326.4 (41.1)</td>
<td>293.8 (73.9)</td>
<td>5.53</td>
<td>.001*</td>
<td>.30</td>
<td>79.46 &lt; .001</td>
<td>3.38</td>
</tr>
<tr>
<td>Rapid eye movement sleep, minutes</td>
<td>41.7 (21.0)</td>
<td>47.3 (19.6)</td>
<td>39.0 (20.1)</td>
<td>34.5 (23.1)</td>
<td>1.30</td>
<td>.23</td>
<td>.15</td>
<td>68.24 &lt; .001</td>
<td>3.00</td>
</tr>
<tr>
<td>Sleep onset latency, minutes</td>
<td>31.4 (30.1)</td>
<td>22.6 (21.1)</td>
<td>19.4 (12.3)</td>
<td>19.2 (17.4)</td>
<td>3.41</td>
<td>.02</td>
<td>.23</td>
<td>44.12 &lt; .001</td>
<td>1.46</td>
</tr>
</tbody>
</table>

* Adjusted means are means adjusted for baseline differences; these means are different from the raw means displayed in Table 4.

† Significant after Bonferroni correction.

Sleep efficiency was calculated as sleep duration divided by time spent in bed multiplied by 100.

Sleep onset latency was measured as elapsed time from time of lights out to first epoch scored as sleep.

ES = effect size; P-value derived from ANCOVA t-test; f = effect size derived from the ANCOVA pairwise comparison t-test; f = √(ETA²(1 − ETA²); ES (d) = effect size (Cohen’s d) = ABS ($E_{p} − E_{c}$) / σ.

Combined Strength Training and Walking Reduces the Apnea-Hypopnea Index

- **Secondary Data Analysis:** N = 144
  - residents who exercised (EG, n=97)
  - usual care control group (n=47)
- **Primary Outcome:** apnea-hypopnea index (AHI)
- **Results:**
  - Adjusted for the baseline AHI, ANCOVA showed a significant decrease in AHI for the EG compared with the control group. The adjusted means showed a decrease in mean AHI from 20.2 (SD `1.39) to 16.7 (SD `0.96) for a group mean reduction of 17.3%.
  - No significant association of gains in arm or leg strength with change in AHI

Additional Benefit of Exercise plus Social Activity

- Improved function
  - Significant improvements in the social activity plus exercise group over the social activity group (95% confidence interval, -3.94 to -0.97) and the usual care group (95% confidence interval, -3.69 to -0.64).
  - Sleep-based mechanism
    - However, no significant relationship between change in function and change in any sleep quality parameter

Obstructive Sleep Apnea
Determine if treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) in persons with mild cognitive impairment delays their cognitive decline and preserves everyday function.

Specific Aims:
- Determine feasibility of the study methods
- Estimate effect sizes for a larger definitive study
- Validate neuroimaging biomarkers

Richards KC R01 AG034682
## Results: Sleep and Nighttime Agitation

Best fitting multiple linear regression model predicting Behavioral Disturbance Index

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$r$ ($p$-value)</th>
<th>Coeff</th>
<th>SE</th>
<th>t</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-RLS</td>
<td>0.31(0.02)</td>
<td>0.70</td>
<td>0.23</td>
<td>3.0</td>
<td>0.004</td>
</tr>
<tr>
<td>MMSE</td>
<td>-0.33 (0.012)</td>
<td>-0.04</td>
<td>0.007</td>
<td>-2.79</td>
<td>0.012</td>
</tr>
<tr>
<td>Log AHI</td>
<td>-0.37 (0.004)</td>
<td>-0.32</td>
<td>0.11</td>
<td>-3.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td>2.95</td>
<td>0.39</td>
<td>7.51</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Adjusted $R^2 = 0.31; p = 0.0000$

# Periodic Leg Movements Predict Total Sleep Time

<table>
<thead>
<tr>
<th>Predictors</th>
<th>( \beta \text{hat} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Bed</td>
<td>0.85*</td>
</tr>
<tr>
<td>Age</td>
<td>-2.37**</td>
</tr>
<tr>
<td>Periodic Leg Movement Index</td>
<td>-0.72**</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>0.4363*</td>
</tr>
</tbody>
</table>

p<0.001; **p<0.05, \( R^2 \) is the proportion of the variation in TST explained by the model; \( \beta \text{hat} \) is the estimated coefficient of the predictor in the given multivariate linear regression model

RLS and Nighttime Agitation in Older Adults with Cognitive Impairment

- RLS infrequently recognized and diagnosed in persons with dementia/mild cognitive impairment
- Lack of RLS diagnostic tool suitable for persons who lack the cognitive abilities to report complex symptoms

RESTLESS LEGS SYNDROME

Diagnostic Accuracy of Behavioral, Activity, Ferritin, and Clinical Indicators of Restless Legs Syndrome

Kathy C. Richter, MD, PhD, RN, FAN, James E. Ebert, MD, PhD, Vanessa E. Hoger, MD, MS, Chad E. Johnson, MD, PhD, FAN, Lori G. Hauk, MS, DMSc, MPH, FPCP. Cen-Lin Ke, MD, PhD, Donald F. Lieberman, MD, PhD, Cen-Lin Ke, MD, PhD, FAN, Vanessa E. Hoger, MD, MS, Chad E. Johnson, MD, PhD, FAN, Lori G. Hauk, MS, DMSc, MPH, FPCP.

Study Objective: To validate diagnostic measures of restless legs syndrome (RLS) in persons with dementia, as well as to determine the cognitive ability to report complex symptoms, required RLS intervention and research in this population. The aim of this study was to determine the sensitivity and specificity of existing measures of RLS in those with dementia.

Methods: The Mini-Mental State Examination (MMSE), the MMSE, the Mini-Mental State Examination-2 (MMSE-2), and the Mini-Mental State Examination-3 (MMSE-3) were used to assess cognitive function. The MMSE-3 was used to assess cognitive function in persons with dementia. The MMSE-2 was used to assess cognitive function in persons with dementia who were able to complete the MMSE-3.

Results: The MMSE-3 was the best measure for assessing cognitive function in persons with dementia who were able to complete the MMSE-3.

Conclusions: The MMSE-3 was the best measure for assessing cognitive function in persons with dementia who were able to complete the MMSE-3.

Restless Legs Syndrome (RLS) is a common symptom that occurs in persons with dementia and is associated with a variety of factors, including sleep disturbances, mood disorders, and decreased physical activity. The diagnosis of RLS in persons with dementia is challenging, as they may have difficulty reporting their symptoms or understanding the instructions.

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Conclusions: The MMSE-3 was the best measure for assessing cognitive function in persons with dementia who were able to complete the MMSE-3.
Fig. 3. Recommended algorithm for management of sleep disturbances in residents with dementia (nursing homes in the canton of Fribourg). *Light therapy; warm drink; limit fluid intake before bedtime; expose to bright day light or other approaches. †Take into a...

Isabelle Anguish, Jean-François Locca, Christophe Büla, Serge Zumbach, Olivier Bugnon

**Pharmacologic Treatment of Behavioral and Psychological Symptoms of Dementia in Nursing Homes: Update of the 2008 JAMDA Recommendations**

Journal of the American Medical Directors Association, Volume 16, Issue 6, 2015, 527–532

http://dx.doi.org/10.1016/j.jamda.2015.03.014
EXERCISE AND SLEEP KNOWLEDGE GAPS

- Few well designed studies using objective sleep outcome measures
- Few studies have examined common sleep disorders in institutionalized elders and potential interactions with exercise
- Few studies have examined interactions with cognition and other pathways
- Lack of data on duration, frequency, intensity, type, time of day
- Little information on the clinical significance of the effect of exercise on the AHI (nocturia, daytime sleepiness)
KNOWLEDGE GAPS

- Inadequate representation of diverse races and ethnicities in nursing home sleep research
- Little knowledge on effects of treatment of sleep apnea
SLEEPING WOMAN BY MAN RAY

RESEARCH OPPORTUNITIES
RESEARCH OPPORTUNITIES

1) Concurrently address sleep disturbance and commonly occurring comorbid chronic conditions and examine interactions

2) Design clinical trials tailored to specific causes for sleep disturbance and examine causal mechanisms
**TAILORED LIGHTING INTERVENTION**

**Sample:** 14 residents of skilled nursing homes (with dementia)

**Primary Outcomes:** sleep, agitation, and depression

**Design:** 4-week, low-level bluish-white lighting intervention

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A digital timer was programmed to automatically turn on all luminaires close to the time each resident woke up and off at 6 pm.

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**Research Opportunities**

3) Diagnose and treat sleep disorders in institutionalized elderly and examine cognitive, functional, and quality of life outcomes

- Restless legs syndrome (sundowning, nocturnal wandering)
- Obstructive sleep apnea (cognition, quality of life, function)

4) Develop/validate/refine measures of sleep disturbance for persons with limited cognitive and verbal abilities

5) Examine relationships between sleep disturbance and co-morbid delirium


RECOMMENDATIONS FOR IMPROVING THE QUALITY OF CLINICAL TRIALS TO DETERMINE THE EFFECT OF INTERVENTIONS ON SLEEP IN INSTITUTIONALIZED ELDERLY

- Use well-characterized sample, specific dementia diagnosis, genotyping
- Control as many confounding variables as possible
- Use an RCT design and placebo control, if possible
- Analyze planned (apriori) outcome measures guided by conceptual model
- Actigraphy
  - ≥7 nights
  - Use parameters related to sleep, activity, and circadian rhythms
  - Identify actigraphy parameters that are clinically most important for primary sleep outcome
  - Use primary sleep outcome as inclusion criteria
- Polysomnography
  - Multiple nights
  - Modified scoring criteria for dementia
OUR FANTASTIC TEAM

- Nalaka Gooneratne, MD
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- Amy Sawyer PhD, RN
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- Corinne Lambert, PhD, RN

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- Paofeng Tsai, PhD, RN
- Mort Kleban, PhD
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