Melatonin for Circadian Rhythm Disturbances in Dementia

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Objectives

1. Describe the pathophysiology of circadian rhythm disturbances in dementia
2. Evaluate current treatment options for circadian rhythm disturbances in dementia
3. Review available literature on the use of melatonin in dementia
4. Determine melatonin’s role in the treatment of circadian rhythm disturbances in dementia
I. Dementia

a. Definition and epidemiology\(^1\text{--}^3\)
   i. Chronic, acquired decline in memory and at least one other cognitive function (e.g. language, motor, executive) sufficient to impair daily functioning (see Appendix A)
   ii. Incidence increases with age from 13% in people over the age of 65 years to 50% in people over the age of 85 years

b. Types and pathophysiology\(^1\text{--}^3\)
   i. Alzheimer’s disease (see Figure 1)
      1. Secondary to amyloid plaques (insoluble deposits of beta-amyloid protein) and neurofibrillary tangles (abnormal aggregates of tau protein)
      2. Characterized by insidious onset and impaired memory and functioning
   ii. Lewy body dementia
      1. Secondary to Lewy bodies (abnormal aggregates of alpha-synuclein)
      2. Characterized by visual hallucinations, delirium, parkinsonism, and falls
   iii. Vascular dementia
      1. Secondary to cerebrovascular disease
      2. Characterized by abrupt onset and decline in executive function
   iv. Frontotemporal dementia
      1. Secondary to Pick inclusion bodies (abnormal aggregations of tau protein)
      2. Characterized by personality changes and behavioral disinhibition
   v. Other causes
      1. Parkinson’s disease or Huntington’s disease
      2. Human immunodeficiency virus (HIV) or Creutzfeld-Jakob disease
      3. Traumatic brain injury, brain tumor, or hydrocephalus
      4. Hypothyroidism, vitamin B\(_{12}\) deficiency, alcohol abuse, or mixed etiology

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{alzheimer_disease_pathophysiology.png}
\caption{Pathophysiology of Alzheimer’s Disease\(^4\)}
\end{figure}
II. The Normal Sleep-Wake Cycle

a. Circadian rhythm\(^5-7\)
   i. Twenty-four hour physiologic pattern of rest and activity
   ii. Regulated by secretion of melatonin from the pineal gland
b. Suprachiasmatic nucleus (SCN) – “biological clock” (see Figure 2)\(^5-7\)
   i. Located in the hypothalamus and responsible for regulation of circadian rhythm
   ii. Receives signals from the retina regarding exogenous light exposure
c. Pineal gland (see Figure 2)\(^5-7\)
   i. Located in the epithalamus and responsible for production and secretion of melatonin
   ii. Melatonin secretion is regulated by the SCN and sympathetic nervous system
d. Melatonin\(^5-7\)
   i. Endogenous hormone biosynthesized from serotonin in the pineal gland
   ii. Release is stimulated by darkness and inhibited by bright light
   iii. Under normal conditions, circulating levels will rise 2 hours before usual bedtime and remain elevated throughout the night to promote sleep
   iv. Inversely related to core body temperature (another marker of circadian rhythm)

![Figure 2. The Suprachiasmatic Nucleus and Pineal Gland](image)

e. Stages of sleep\(^9\)
   i. Non-rapid eye movement (Non-REM) sleep (60 to 90 minutes)
      1. Stage 1 – lightest sleep, activity decreases, eyes close, easy to awaken
      2. Stage 2 – light sleep, muscles become relaxed
      3. Stage 3 – deep sleep, heart rate, respirations, and temperature decrease
      4. Stage 4 – deepest sleep, restorative, difficult to awaken
   ii. Rapid eye movement (REM) sleep (10 to 40 minutes)
      1. Rapid eye movement, heart and respiratory rate increase, muscles relaxed
      2. Brain activity is heightened to level of wakefulness, dreaming occurs
   iii. Cycles of non-REM followed by REM sleep normally occur four to five times per night
III. Circadian Rhythm Disturbances in Dementia

a. Epidemiology\textsuperscript{5,10}
   i. Incidence is estimated at greater than 60\% in severely demented patients
   ii. Most common in Lewy body dementia and Alzheimer’s disease

b. Pathophysiology\textsuperscript{6,11,12}
   i. Advanced age and dementia result in neurodegenerative changes that cause a progressive deterioration in circadian rhythm
      1. Reduced melatonin production from the pineal gland
      2. Alterations in expression of melatonin receptors in SCN
      3. Decreased ability for the retina and optic nerve to transmit light
   ii. Circadian rhythms become more chaotic and irregular (see Figure 3)
      1. Directly correlated to age and severity of cognitive decline
      2. Results in temporal changes in mood, rest, and activity

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure3}
\caption{Temperature and Motor Activity Patterns in Alzheimer’s Disease\textsuperscript{13}}
\end{figure}

c. Contributing factors\textsuperscript{10}
   i. Inadequate exposure to light during the day
   ii. Unmet physical or psychological needs (e.g. pain, discomfort)
   iii. Shift changes/changes in staffing in institutional settings
   iv. Decreased availability or neglect from caregivers in home settings
   v. Difficulty breathing during sleep (e.g. sleep apnea)
   vi. Noisy environment/frequent nighttime interruptions
   vii. Sensory impairments (e.g. vision, hearing)
   viii. Lack of structured stimulation during the day leading to boredom
   ix. Underlying psychiatric illness (e.g. schizophrenia)
   x. Unfamiliar visitors or altercations with other residents
   xi. Medications (e.g. adverse effects, timing of administration)
d. **Clinical presentation**\(^5,10\)
   i. Decrease in total sleep time and impaired sleep quality or efficiency
      1. Increased time in light sleep = more easily awakened
         a. Decreased sleep maintenance and early morning awakenings
         b. Increased nocturnal motor activity and nocturnal wandering
      2. Decreased time in deep sleep = less restorative sleep
         a. Excessive daytime fatigue and decreased daytime alertness
         b. Further impairment of cognitive function and decreased immunity
      3. Decreased time in REM sleep = REM sleep disorders
         a. Loss of muscle relaxation during REM sleep
         b. May exhibit violent physical activity while dreaming
   ii. Additional symptoms (see Table 1)

| Table 1. Symptoms of Dementia Related to Circadian Rhythm Disturbances\(^5,10,14\) |
|---------------------------------|-------------------------------------------------|
| **Sleep Disturbances**          | Insomnia                                        |
|                                 | Nocturnal wandering                             |
|                                 | Early morning awakenings                        |
|                                 | Excessive daytime fatigue                      |
| **Behavioral Disturbances**     | Agitation/aggression                            |
|                                 | Loud vocalizations                              |
|                                 | Motor restlessness                              |
|                                 | Delirium/sundowning\(^a\)                       |
| **Depression**                  | Apathy                                          |
|                                 | Irritability                                    |
|                                 | Anxiety                                         |
|                                 | Decreased appetite                              |
| **Psychosis**                   | Visual hallucinations                           |
|                                 | Delusions                                       |

\(^a\) Refers to agitation or delirium that occurs in relation to a specific time of day (typically during the late afternoon/early evening)

e. **Complications**\(^5,10\)
   i. Progressive worsening of cognitive impairment and circadian rhythm (see Figure 4)
   ii. Increased caregiver burden and stress
   iii. Increased likelihood of institutionalization
   iv. Risk of harm to self or others
   v. Decreased quality of life and life expectancy

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**Figure 4. Progressive Worsening of Circadian Rhythm in Dementia**
IV. Current Treatment Options for Circadian Rhythm Disturbances in Dementia

a. Non-pharmacological therapy (see Table 2)
   i. Minimize contributing factors
   ii. Encourage good sleep hygiene

Table 2. Non-Pharmacological Therapy for Circadian Rhythm Disturbances in Dementia\textsuperscript{5,10,14-16}

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Optimize treatment of underlying diseases (e.g. pain, restless leg syndrome, sleep apnea)</td>
<td>Provide reassurance and redirection for undesirable behaviors and reinforce desirable behaviors</td>
</tr>
<tr>
<td>Provide adequate caregiver support to meet physical, psychological, and social needs</td>
<td>Create quiet and comfortable sleeping environment at night (e.g. minimize noise, limit interruptions)</td>
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<td>Develop a structured daily routine (e.g. regular times for waking, eating, sleeping)</td>
<td>Limit evening fluid intake and empty bladder before going to bed to minimize nocturia</td>
</tr>
<tr>
<td>Offer daytime recreational therapy (e.g. music therapy, pet therapy)</td>
<td>Provide adequate exposure to bright light during the day and darkness at night</td>
</tr>
<tr>
<td>Increase physical activity during the day (e.g. exercise) and limit daytime napping</td>
<td>Avoid caffeine, alcohol, and nicotine intake</td>
</tr>
</tbody>
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iii. Bright light therapy\textsuperscript{17}
   1. Purposeful exposure to bright light during the day
      a. Stimulates the SCN to resynchronize circadian rhythm
      b. Hypothesized to improve sleep, mood, cognition, and behavior
   2. Variety of interventions have been studied
      a. Exposure to a light box placed in the visual field
      b. A light visor worn on the head
      c. Ceiling mounted light fixtures
      d. "Naturalistic" lighting that mimics dawn-dusk patterns
   3. Controlled trials have yielded inconsistent results
      a. Possibly due to significant heterogeneity of design
      b. Differences in types and severities of dementia, types of light intervention, timing and or length of light exposure
   4. Systematic review by the Cochrane Collaboration\textsuperscript{17}
      a. Reviewed ten randomized controlled trials (RCTs) evaluating the use of light therapy (any intensity and duration) in dementia
      b. “There is insufficient evidence to determine whether light therapy is effective in the management of cognitive, sleep, functional, behavioral, or psychiatric disturbances in dementia.”
b. Pharmacological therapy (see Table 3)
   i. Guidelines from the American Geriatric Society (AGS)\(^2,14\) and American Psychiatric Association (APA)\(^3\) recommend non-pharmacological therapy first-line
   ii. When necessary, pharmacological therapy in dementia should be individualized based on target symptoms, adverse effects, drug interactions, etc.

Table 3. Pharmacological Therapy for Circadian Rhythm Disturbances in Dementia\(^{18-35}\)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potential Benefits</th>
<th>Potential Risks</th>
</tr>
</thead>
</table>
| Acetylcholinesterase inhibitors (e.g. donepezil, galantamine, and rivastigmine)\(^{18-23}\) | - FDA approved for mild, moderate, and severe dementia  
- Considered most efficacious in Lewy body dementia  
- May improve cognition, mood, and behavior, but effects are modest | - Adverse effects: nausea/vomiting, diarrhea, dyspepsia, anorexia, insomnia, bradycardia, and vivid dreams |
| NMDA receptor antagonist (e.g. memantine)\(^{18-21,24-26}\) | - FDA approved for moderate and severe dementia  
- May improve cognition, mood, and behavior, but effects are modest | - Adverse effects: dizziness, headache, confusion, but overall well tolerated |
| Antidepressants (e.g. SSRIs, mirtazapine, and trazodone)\(^{18-21,27}\) | - May promote sleep, improve mood, and decrease irritability  
- Ideal for patients with comorbid depression | - Adverse effects: nausea/vomiting, diarrhea, insomnia, and falls |
| Sedative hypnotics (e.g. short-acting benzodiazepines and zolpidem)\(^{18-19}\) | - May promote sleep and decrease anxiety and agitation  
- Ideal for as needed dosing  
- Variety of agents and dosage forms | - Adverse effects: falls, cognitive impairment, and respiratory depression  
- May cause disinhibition (paradoxical increase in agitation and confusion)  
- Risk of dependency |
| Antipsychotics (e.g. risperidone, quetiapine, and olanzapine)\(^{18-21,28-35}\) | - May improve agitation, promote sleep, and treat hallucinations and delirium, but effects are modest  
- Variety of agents and dosage forms | - Adverse effects: cerebrovascular events, extrapyramidal symptoms, metabolic changes, anticholinergic effects, and orthostasis  
- FDA Black Box Warning for increased mortality in dementia  
- May exacerbate sleep-wake disturbances (haloperidol)  
- Not recommended in Lewy body dementia (increased sensitivity to adverse effects)  
- Based on results of CATIE-AD trial, risks may outweigh benefits |
| Anticonvulsants (e.g. carbamazepine and valproic acid)\(^{18-21}\) | - May improve mood and behavior, but effects are modest | - Adverse effects: ataxia, falls, confusion, bone marrow suppression, and hepatotoxicity  
- Multiple drug interactions |

Key: FDA = Federal Food and Drug Administration, NMDA = N-Methyl-D-Aspartic acid, SSRI = selective serotonin reuptake inhibitor, CATIE-AD = Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease
V. Melatonin

a. Mechanism of action\textsuperscript{36}
   i. Synthetic supplement of hormone involved in synchronization of circadian rhythm
   ii. Increases the binding of gamma-aminobutyric acid (GABA) to its receptors
   iii. Produces rapid and transient sleep-inducing effect (decreases sleep onset latency)
   iv. Indirectly improves behavior and mood by improving sleep quality
   v. Additionally, proposed to have antioxidant and neuroprotective properties

b. Pharmacokinetics\textsuperscript{37-38}
   i. Oral bioavailability is low (approximately 15%) due to extensive first-pass metabolism in addition to high individual variability
   ii. Time to peak concentrations varies from 30 to 180 minutes with immediate-release preparations and is up to 3 hours with sustained-release preparations
   iii. Metabolized hepatically via cytochrome P450 1A1, 1A2, and 2C19 to inactive metabolites, which are then renally eliminated
   iv. Elimination half-life is approximately 45 minutes with immediate-release preparations and up to 4 hours with sustained-release preparations

c. Cost and availability\textsuperscript{38-40}
   i. Available in the United States as a dietary supplement sold over-the-counter (OTC)
      1. Immediate-release (IR) and sustained-release (SR) products in doses ranging from 0.1 mg to 10 mg from various manufacturers
      2. Cost from drugstore.com: $5-10/60-count bottle ($0.08-0.16/dose)
      3. Inconsistency in formulations creates variable pharmacokinetics
   ii. Available in the United Kingdom as prescription drug under the trade name Circadin\textsuperscript{®}
      1. Prolonged-release 2 mg product manufactured by Neurim Pharmaceuticals
      2. Approved by the European Medicines Agency (EMA) as monotherapy for the short-term treatment (up to 13 weeks) of primary insomnia characterized by poor quality of sleep in patients age 55 years and over

d. Efficacy and safety
   i. Studies were selected for review if they were RCTs, included patients with dementia/cognitive impairment, and evaluated the use of melatonin alone or in combination with bright light therapy for behavioral and/or sleep disturbances
      1. Tables 4 and 6 provide summaries of the RCTs for melatonin alone and in combination with bright light therapy, respectively
      2. Tables 5 and 7 provide summaries of the two largest RCTs evaluating melatonin alone and in combination with bright light therapy, respectively
   ii. Important outcome measures
      1. Sleep quality by wrist actigraph
         a. Consists of a small recorder worn on patient’s wrist
         b. Measures periods of rest and activity based on movement
         c. Established method for studying sleep-wake cycles in dementia
      2. Rating Scales (see Appendix B)
         a. Cognitive function (e.g. MMSE, ADAS-cog)
         b. Activities of daily living (e.g. ADCS-ADL, NI-ADL)
         c. Neuropsychiatric symptoms (e.g. NPI)
         d. Behavior and agitation (e.g. CMAI, MOSES)
         e. Mood and depression (e.g. CSDD, PGCARS)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects</th>
<th>Setting</th>
<th>Interventions</th>
<th>Duration</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serfaty⁴¹</td>
<td>Single-center, randomized, double-blind, placebo-controlled, crossover trial</td>
<td>25 patients with dementia and sleep disturbance</td>
<td>Home or institution (England)</td>
<td>Melatonin SR 6 mg¹</td>
<td>2 x 2 weeks</td>
<td>Sleep quality (wrist actigraph) Melatonin had no effect on total sleep time, number of awakenings, or sleep efficiency</td>
</tr>
<tr>
<td>Asayama⁴²</td>
<td>Single-center, randomized, double-blind, placebo-controlled, parallel trial</td>
<td>18 patients with probable Alzheimer’s disease</td>
<td>Institution (Japan)</td>
<td>Melatonin IR 3 mg¹</td>
<td>4 weeks</td>
<td>Sleep quality (wrist actigraph) Melatonin improved mean nocturnal sleep time by 33.2% vs. -0.2% for placebo (p = 0.017) and decreased mean nocturnal activity counts by 44.9% vs. 29.8% for placebo (p = 0.014), but did not result in statistically significant changes in daytime sleep or activity counts Non-cognitive functions (ADAS non-cog) Melatonin improved scores by 4.1 vs. 0.8 for placebo (p = 0.002)</td>
</tr>
<tr>
<td>Singer⁴³</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, parallel trial</td>
<td>157 patients with probable Alzheimer’s disease and sleep disturbance</td>
<td>Home or institution (USA)</td>
<td>Melatonin SR 2.5 mg¹</td>
<td>8 weeks</td>
<td>Sleep quality (wrist actigraph and SQR) Melatonin had no effect on total sleep time, time awake after sleep onset, sleep efficiency, but SQR improved from “difficult” to “fair” for melatonin SR 2.5 mg vs. placebo (p = 0.03) Neuropsychiatric symptoms (NPI) Melatonin SR 2.5 mg showed a statistically significant improvement over placebo (-6.4 vs. -0.17, p = 0.047)</td>
</tr>
<tr>
<td>Gehrman⁴⁴</td>
<td>Single-center, randomized, double-blind, placebo-controlled, parallel trial</td>
<td>41 patients with probably Alzheimer’s disease</td>
<td>Institution (USA)</td>
<td>Melatonin 10 mg (8.5 mg IR and 1.5 mg SR)¹</td>
<td>10 days</td>
<td>Sleep quality (wrist actigraph) Melatonin had no effect on total nighttime or daytime sleep, wake time after sleep, or sleep efficiency Agitation (ABRS and CMAI) Melatonin had no effect on ABRS or CMAI ratings</td>
</tr>
</tbody>
</table>

¹ Diagnosis of dementia/Alzheimer’s disease by DSM-IV-TR and NINCDS-ADRDA criteria (see Appendix A)  
² Melatonin and placebo given every night at bedtime
Table 5. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer’s disease


Design
- Multicenter, randomized, double-blind, placebo-controlled trial conducted in the US

Intervention
- Placebo, melatonin SR 2.5 mg, or melatonin IR 10 mg taken 1 hour prior to habitual bedtime (duration 8 weeks)

Subjects
Inclusion Criteria:
- Probable Alzheimer’s disease (NINCDS-ADRDA)
- Nighttime sleep disturbance (greater than 2 weeks)
- Consistent, reliable caregiver
- Ability to comply with protocol

Exclusion Criteria:
- Sleep disturbance due to acute illness, delirium, or pain
- Clinically significant movement disorder
- Unstable medical condition
- Severe agitation

Outcomes
Primary Outcomes:
- Sleep quality measured by wrist actigraph
  - NTST – nighttime sleep time, total sleep time (min) between 8pm and 8am
  - DTST – daytime sleep time, total sleep time (min) between 8am and 8pm
  - DTST/NTST – ratio of daytime to nighttime sleep
  - WASO – wake after sleep onset or time awake (min) after sleep onset between 8pm and 8am
  - SE% – percentage of time asleep between 8pm and 8am
- Gained > 30 min – percentage of patients with a least 30 min increase in NTST

Secondary Outcomes:
- Sleep quality rating (SQR) by caregiver, cognitive function (MMSE, ADAS-cog), activities of daily living (ADCS-ADL inventory), depression (HAM-D), neuropsychiatric symptoms (NPI and SDI), and adverse events

Statistics
Power:
- 50 subjects per treatment arm needed to detect a 30 min change in NTST with 80% power and 2-sided alpha 0.05

Statistical Tests:
- Mann-Whitney t test, Chi square test, Fisher exact test, Holm adjustment

Results
Baseline Characteristics: (n = 157)
- Mean age 77.4 ± 8.9 years, duration of dementia 4.9 ± 3 years, MMSE 13.9 ± 8.8, and ADAS-cog 38.5 ± 18.9
- No differences between groups at baseline except NPI scores were highest in melatonin SR 2.5 mg group

Primary Outcomes:
- Trends towards increased NTST and percent who gained > 30 min NTST for melatonin vs. placebo (see Table 5a), but no significant differences between treatment groups for change in any of the primary sleep measures

Secondary Outcomes:
- Melatonin SR 2.5 mg demonstrated a statistically significant improvement over placebo in SQR by caregiver (change from “difficult night” to “fair night”) and NPI (see Table 5a)
- There were no other statistically significant differences between treatment groups for change in any of the secondary outcome measures, including adverse events

Table 5a. Mean change in outcome measures from baseline to 8 weeks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n = 52)</th>
<th>Melatonin SR 2.5 mg (n = 54)</th>
<th>Melatonin IR 10 mg (n = 51)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTST (min)</td>
<td>3 ± 39</td>
<td>13 ± 44</td>
<td>16 ± 54</td>
<td>&gt; 0.05abc</td>
</tr>
<tr>
<td>Gained &gt; 30 min (%)</td>
<td>20%</td>
<td>24%</td>
<td>37%</td>
<td>0.07a</td>
</tr>
<tr>
<td>NPI</td>
<td>-0.2 ± 14</td>
<td>-6.4 ± 15</td>
<td>0.5 ± 12</td>
<td>&lt; 0.05bcd</td>
</tr>
<tr>
<td>SQR</td>
<td>0.3 ± 0.6</td>
<td>0.4 ± 0.7</td>
<td>0.2 ± 0.4</td>
<td>0.03bcd</td>
</tr>
</tbody>
</table>

Melatonin 10 mg IR vs. placebo, Melatonin SR 2.5 mg vs. placebo, Melatonin SR 2.5 mg vs. melatonin IR 10 mg

Conclusions
- In patients with Alzheimer’s disease and sleep disturbance, melatonin given at bedtime resulted in no improvement in overall sleep quality, cognitive function, or behavioral disturbances, but was as well tolerated as placebo

Critique
Strengths:
- Multicenter, randomized, double-blind design
- Intention-to-treat analysis
- Some standardized assessment scales (e.g. NPI)
- Large sample size (met power) and adequate duration

Limitations:
- External validity in other types of dementia
- Some non-standardized assessment scales (e.g. SQR)
- Higher NPI scores at baseline for melatonin SR 2.5 mg
- Lack of information regarding adverse events
Table 6. RCTs for Combination Melatonin and Bright Light Therapy for Circadian Rhythm Disturbances in Dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects</th>
<th>Setting</th>
<th>Interventions</th>
<th>Duration</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Haffmans\(^{45}\)      | Single-center, randomized, double-blind,    | 6 patients with dementia\(^ {a} \) and disturbed behavior including motor restlessness | Institution (Netherlands)            | - Bright light\(^ {b} \) and melatonin IR 2.5 mg\(^ {c} \)  
- Bright light and placebo | 2 weeks  | - Motor restlessness (CGI and GIP)  
Bright light and placebo resulted in a significant decrease in motor restlessness from baseline on CGI (5.0 to 3.7, \( p = 0.049 \)), GIP 10 item 3 (2.9 to 1.9, \( p = 0.007 \)), GIP 10 item 5 (2.6 to 1.5, \( p = 0.01 \)); no significant changes with combination bright light and melatonin were observed |
| Dowling\(^{46}\)       | Multicenter, randomized, double-blind,      | 50 patients with probable Alzheimer’s disease\(^ {a} \) and rest-activity disturbance | Institution (USA)                    | - Bright light\(^ {d} \) and melatonin IR 5 mg\(^ {e} \)  
- Bright light and placebo  
- No intervention | 10 weeks | - Sleep-wake/rest-activity (wrist actigraph)  
Bright light plus melatonin resulted in a significant improvement in daytime sleep \(( p < 0.001 \)), daytime activity \(( p = 0.04 \)), day:night sleep ratio \(( p < 0.001 \)), rest-activity rhythm amplitude \(( p = 0.002 \)), and average activity during 10 most-active hours \(( p = 0.03 \)); no significant difference in nighttime sleep variables were observed between groups |
| Riemersma-van der Lek\(^{47}\) | Multicenter, randomized, double-blind,      | 189 elderly patients (87% with diagnosis of dementia) | Institution (Netherlands)            | - Bright light\(^ {f} \) and melatonin IR 2.5 mg\(^ {c} \)  
- Bright light and placebo  
- Regular light and melatonin IR 2.5 mg  
- Regular light and placebo | 15 months | - Sleep quality (wrist actigraph)  
Melatonin decreased sleep onset latency by 8.2 minutes \(( CI 1.08-15.35, \ p = 0.02 \)), increased sleep duration by 27 minutes \(( CI 9-46, \ p = 0.004 \)); combination light and melatonin therapy increased sleep efficiency by 3.5% \(( CI 0.8-6.1\%), \ p = 0.01 \) and improved nocturnal restlessness by 1 min/hr \(( CI 0.26-1.78, \ p = 0.01 \))  
- Non-cognitive function (CSDD, CMAI, NI-ADL)  
Light decreased depressive symptoms on CSDD by 1.47 points \(( CI 0.24-2.70, \ p = 0.02 \)); combination therapy decreased aggressive behavior on CMAI by 3.9 points \(( CI 0.88-6.92, \ p = 0.01 \))  
- Adverse effects  
No increase in occurrence of adverse effects with melatonin or light versus placebo was observed |

\(^ {a} \) Diagnosis of dementia/Alzheimer’s disease by DSM-IV-TR and NINCDS-ADRDA criteria (see Appendix A)  
\(^ {b} \) Bright light exposure via light device for 30 minutes every morning  
\(^ {c} \) Melatonin and placebo given every night at bedtime  
\(^ {d} \) Bright light exposure via natural light or light box for one hour every Monday-Friday morning  
\(^ {e} \) Melatonin and placebo given every evening with dinner  
\(^ {f} \) Bright light exposure via ceiling-mounted fixtures left on between 9am and 6pm in common living room of group care facilities
Melatonin for circadian rhythm disturbances in dementia

Table 7. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities


**Design**
- Multicenter, randomized, double-blind, placebo-controlled trial conducted in the Netherlands

**Intervention**
- Daytime bright light plus melatonin IR 2.5 mg or placebo given 1 hour before bedtime (mean follow-up: 15 months)

**Subjects**

<table>
<thead>
<tr>
<th>Inclusion Criteria:</th>
<th>Exclusion Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly residents of 12 Dutch group care facilities</td>
<td>Aphakia or severe liver or kidney dysfunction</td>
</tr>
</tbody>
</table>

**Outcomes**

| Sleep quality measured by wrist actigraph (sleep efficiency, sleep onset latency, and total sleep duration) | 
| Cognition (MMSE), mood (CSDD, PGCARS, PGCMs), behavior (MOSES, NPI, CMAI), and functioning (NI-ADL) | 
| Assessed at baseline, 6 weeks, then every 6 months up to 3.5 years |

**Statistics**

| Power: | 
| 147 participants needed to detect an effect size of 0.25-0.35 with 80% power and 2-sided alpha of 0.05 |
| Statistical Tests: | 
| Mixed-effects regression analysis, t test, Chi square test, and logistic regression |

**Baseline Characteristics:** (n = 189)
- Mean age 85.8 ± 5.5 years, 90% female, 63% Alzheimer’s disease, 11% vascular dementia, 13% other dementias
- No differences between treatment groups at baseline

**Outcomes:** (see Table 7a)
- Light increased total sleep time and improved scores on MMSE, CSDD, and NI-ADL
- Melatonin alone increased total sleep time, decreased sleep onset latency, and increased uninterrupted sleep
- Melatonin alone adversely affected mood and behavior on PGCARS and MOSES, respectively; however, PGCARS and CMAI scores were improved when melatonin was used in combination with bright light
- Combination melatonin and bright light improved sleep efficiency as well as nocturnal restlessness and awakenings
- No significant adverse effects, and no significant differences between prescription of psychotropic medications

**Table 7a. Factorial treatment effect estimates for overall analysis (up to 3.5 years follow-up)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bright Light (n = 49)</th>
<th>Melatonin (n = 46)</th>
<th>Combination (n = 49)</th>
<th>Significant p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.87 (0.04 to 1.71)</td>
<td>-0.01 (-0.79 to 0.76)</td>
<td>-0.23 (-1.38 to 0.93)</td>
<td>0.04a</td>
</tr>
<tr>
<td>CSDD</td>
<td>-1.47 (-2.70 to -0.24)</td>
<td>-0.82 (-1.87 to 0.23)</td>
<td>-0.94 (-2.48 to 0.61)</td>
<td>0.02a</td>
</tr>
<tr>
<td>PGCARS – positive</td>
<td>-0.17 (-0.81 to 0.48)</td>
<td>-0.55 (-1.00 to -0.10)</td>
<td>0.60 (-0.28 to 1.49)</td>
<td>0.02a</td>
</tr>
<tr>
<td>PGCARS – negative</td>
<td>0.50 (-0.07 to 1.07)</td>
<td>0.82 (0.20 to 1.44)</td>
<td>-1.00 (-1.82 to -0.17)</td>
<td>0.01b, 0.02b</td>
</tr>
<tr>
<td>MOSES</td>
<td>-0.51 (-1.55 to 0.53)</td>
<td>1.02 (0.18 to 1.86)</td>
<td>-0.74 (-2.35 to 0.87)</td>
<td>0.02a</td>
</tr>
<tr>
<td>CMAI</td>
<td>-1.61 (-4.82 to 1.60)</td>
<td>1.28 (-1.99 to 4.55)</td>
<td>-3.90 (-6.92 to -0.88)</td>
<td>0.01c</td>
</tr>
<tr>
<td>NI-ADL</td>
<td>-1.77 (-2.92 to -0.61)</td>
<td>-0.92 (-2.33 to 0.49)</td>
<td>-1.25 (-3.13 to 0.63)</td>
<td>0.003a</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>0.83 (-1.89 to 3.55)</td>
<td>1.50 (-1.40 to 4.40)</td>
<td>3.46 (0.84 to 6.09)</td>
<td>0.01c</td>
</tr>
<tr>
<td>Sleep onset latency (min)</td>
<td>-3.61 (-11.23 to 4.01)</td>
<td>-8.23 (-15.38 to -1.08)</td>
<td>-1.17 (-14.3 to 10.8)</td>
<td>0.02a</td>
</tr>
<tr>
<td>Total sleep duration (min)</td>
<td>10.14 (0.38 to 19.90)</td>
<td>27.48 (8.55 to 46.41)</td>
<td>8.46 (27.67 to 44.6)</td>
<td>0.04b, 0.004a</td>
</tr>
<tr>
<td>Night restlessness (min/hr)</td>
<td>-0.25 (-1.47 to 0.97)</td>
<td>-0.48 (-1.62 to 0.66)</td>
<td>-1.00 (-1.78 to -0.26)</td>
<td>0.01c</td>
</tr>
<tr>
<td>Night awakenings (min)</td>
<td>-0.50 (-1.04 to 0.04)</td>
<td>-0.05 (-0.52 to 0.41)</td>
<td>-0.53 (-0.85 to -0.21)</td>
<td>0.01c</td>
</tr>
<tr>
<td>Uninterrupted sleep (min)</td>
<td>0.05 (-4.93 to 5.03)</td>
<td>5.83 (1.05 to 10.61)</td>
<td>-0.15 (-8.30 to 8.00)</td>
<td>0.02a</td>
</tr>
</tbody>
</table>

* Light vs. placebo (regardless of melatonin allocation); ** Melatonin vs. placebo (regardless of light allocation); *** Combination vs. placebo

**Conclusions**
- Increasing light in group care facilities improves cognition, mood, behavior, functional ability, and sleep in residents
- Melatonin improves sleep, but worsens mood and behavior unless used in combination with bright light

**Critique**

<table>
<thead>
<tr>
<th>Strengths:</th>
<th>Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, randomized, double-blind design</td>
<td>External validity (90% female, 13% without dementia)</td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td>High drop-out rate (50% by 1.5 years follow-up)</td>
</tr>
<tr>
<td>Standardized assessment scales</td>
<td>Lack of complete data due to communication difficulties</td>
</tr>
<tr>
<td>Large sample size (met power) and long duration</td>
<td>Unclear for which outcomes power was calculated</td>
</tr>
</tbody>
</table>
iii. Systematic reviews for melatonin in dementia
   a. Cochrane Collaboration\textsuperscript{48}
      i. Evaluated RCTs of melatonin in dementia for impact on cognition, mood, behavior, functions of daily living, and safety
      ii. Included five aforementioned studies by Serfaty\textsuperscript{41}, Asayama\textsuperscript{42}, Singer\textsuperscript{43}, Gehrman\textsuperscript{44}, and Riemersma-van der Lek\textsuperscript{47}
      iii. Authors’ conclusions: there is insufficient data to support the use of melatonin for cognitive impairment in dementia, but results suggest that melatonin has the potential for improve mood and behavior (e.g. NPI and ADAS-noncog scores) in dementia
   b. De Jonghe et al.\textsuperscript{49}
      i. Evaluated RCTs and case series of melatonin in dementia for impact on sleep and sundowning/agitated behavior
      ii. Included five case series and four aforementioned studies by Serfaty\textsuperscript{41}, Asayama\textsuperscript{42}, Singer\textsuperscript{43}, and Gehrman\textsuperscript{44}
      iii. Authors’ conclusions: melatonin may be effective for treatment of sundowning in dementia based on improvement in agitation/behavior in all case series and two of four RCTs
   iv. Potential explanation for negative findings\textsuperscript{41-49}
      1. Neurological deterioration related to advanced dementia may result in decreased expression of melatonin receptors in SCN
      2. Inadequate penetration or concentrations of melatonin at site of action
      3. Inadequate melatonin dose, dosage form, or duration
      4. Population characteristics (type, severity, and duration of dementia)

VI. Summary and Conclusions

a. Circadian rhythm disturbances represent a significant cause of morbidity in dementia
b. Treatment of circadian rhythm disturbances in dementia should be individualized
   i. Non-pharmacological therapy should always be implemented first-line
   ii. Pharmacological therapy should be reserved for severe cases (e.g. harm to self or others) and consist of the lowest effective doses for the shortest necessary duration
   iii. Choice of therapy should be based on target symptoms, adverse effects, drug interactions, and patient-specific factors
c. There is insufficient data to support the use of melatonin for treatment of circadian rhythm disturbances in dementia; however, melatonin remains an attractive treatment strategy for further investigation due to its lack of adverse effects, ease of administration, and cost
## VII. Appendix A: Criteria for Diagnosis of Dementia

### DSM-IV-TR Criteria for the Diagnosis of Dementia of the Alzheimer’s Type

<table>
<thead>
<tr>
<th>A.</th>
<th>The development of multiple cognitive deficits manifested by both:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Memory impairment (impaired ability to learn new information or to recall previously learned information)</td>
</tr>
<tr>
<td>2.</td>
<td>One or more of the following cognitive disturbances:</td>
</tr>
<tr>
<td>a.</td>
<td>Aphasia (language disturbance)</td>
</tr>
<tr>
<td>b.</td>
<td>Apraxia (impaired ability to carry out motor activities despite intact motor function)</td>
</tr>
<tr>
<td>c.</td>
<td>Agnosia (failure to recognize or identify objects despite intact sensory function)</td>
</tr>
<tr>
<td>d.</td>
<td>Disturbance in executive functioning (i.e. planning, organizing, sequencing, abstracting)</td>
</tr>
</tbody>
</table>

### The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

### C. The course is characterized by gradual onset and continuing cognitive decline

### D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

1. Other central nervous system conditions that cause progressive deficits in memory and cognition (e.g. cerebrovascular disease, Parkinson’s disease, Huntington’s disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
2. Systemic conditions that are known to cause dementia (e.g. hypothyroidism, vitamin B₁₂ deficiency, folic acid deficiency, niacin deficiency, hypercalcaemia, neurophilis, HIV infection)
3. Substance-induced conditions

### E. The deficits do not occur exclusively during the course of a delirium

### F. The disturbance is not better accounted for by another Axis I disorder (e.g. major depressive disorder or schizophrenia)

### NINCDS-ADRDA Criteria for Clinical Diagnosis of Alzheimer’s Disease

<table>
<thead>
<tr>
<th>The criteria for clinical diagnosis of PROBABLE Alzheimer’s disease include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia established by clinical examination and documented by the Mini-Mental Test or some similar examination, and confirmed by neuropsychological tests</td>
</tr>
<tr>
<td>Deficits in two or more areas of cognition</td>
</tr>
<tr>
<td>Progressive worsening of memory and other cognitive functions</td>
</tr>
<tr>
<td>No disturbance of consciousness</td>
</tr>
<tr>
<td>Onset between ages 40 and 90, most often after age 65</td>
</tr>
<tr>
<td>Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The clinical diagnosis of PROBABLE Alzheimer’s disease is supported by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia)</td>
</tr>
<tr>
<td>Impaired activities of daily living and altered patterns of behavior</td>
</tr>
<tr>
<td>Family history of similar disorders, particularly if confirmed neuropathologically</td>
</tr>
<tr>
<td>Laboratory results of:</td>
</tr>
<tr>
<td>Normal lumbar puncture as evaluated by standard techniques</td>
</tr>
<tr>
<td>Normal pattern or nonspecific changes in EEG, such as increased slow-wave activity</td>
</tr>
<tr>
<td>Evidence of cerebral atrophy on CT with progression documented by serial observation</td>
</tr>
</tbody>
</table>

### Other clinical features consistent with the diagnosis of PROBABLE Alzheimer’s disease, after exclusion of causes of dementia, include:

| Plateaus in the course of progression of the illness |
| Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss |
| Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder |
| Seizures in advanced disease |
| CT normal for age |

### Features that make the diagnosis of PROBABLE Alzheimer’s disease uncertain or unlikely include:

| Sudden, apoplectic onset |
| Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incontinence early in the course of the illness |
| Seizures or gait disturbances at the onset or very early in the course of the illness |

### Clinical diagnosis of POSSIBLE Alzheimer’s disease:

| May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course |
| May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia |
| Should be used in research studies when a single, gradually progressive, severe cognitive deficit is identified in the absence of other identifiable cause |

### Criteria for diagnosis of DEFINITE Alzheimer’s disease are:

| The clinical criteria for probable Alzheimer’s disease |
| Histopathologic evidence obtained from a biopsy or autopsy |

### Classification of Alzheimer’s disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

| Familial occurrence |
| Onset before age of 65 |
| Presence of trisomy 21 |
| Coexistence of other relevant conditions such as Parkinson’s disease |
### VIII. Appendix B: Summary of Rating Scales Utilized in Trials of Melatonin for Dementia

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Rating Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABRs</td>
<td>Agitation Behavior Rating Scale</td>
<td>56-point scale of agitated behaviors (higher scores indicate more severe agitation)</td>
</tr>
<tr>
<td>ADAS-Cog</td>
<td>Alzheimer’s Disease Assessment Scale – Cognitive</td>
<td>70-point scale of cognitive function (higher scores indicate more severe dementia)</td>
</tr>
<tr>
<td>ADAS-Non-Cog</td>
<td>Alzheimer’s Disease Assessment Scale – Non-Cognitive</td>
<td>50-point scale of non-cognitive function, e.g. mood and behavior (higher scores indicate more severe symptoms)</td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>Alzheimer’s Disease Cooperative Study – Activities of Daily Living</td>
<td>54-point scale of activities of daily living (higher scores indicate higher level of independence)</td>
</tr>
<tr>
<td>CGI</td>
<td>Clinical Global Impression</td>
<td>7-point scale of clinical improvement (1 = very much improved, 4 = no change, 7 = very much worse)</td>
</tr>
<tr>
<td>CMAI</td>
<td>Cohen-Mansfield Agitation Inventory</td>
<td>203-point scale of agitated behaviors (higher scores indicate more severe agitation)</td>
</tr>
<tr>
<td>CSDD</td>
<td>Cornell Scale for Depression in Dementia</td>
<td>38-point scale of depression in dementia (higher scores indicate more severe depression, cutoff = 12)</td>
</tr>
<tr>
<td>GIP 10</td>
<td>Behavioral Rating Scale for Psychogeriatric Inpatients</td>
<td>4-point scale of restless behavior (higher scores indicate more severe symptoms)</td>
</tr>
<tr>
<td>HAM-D</td>
<td>Hamilton Depression Rating Scale</td>
<td>52-point scale of depression (higher scores indicate more severe depression)</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental Status Exam</td>
<td>30-point scale of cognitive function (higher scores indicate higher function, cutoff = 24)</td>
</tr>
<tr>
<td>MOSES</td>
<td>Multi-Observation Scale for Elderly Subjects</td>
<td>34-point scale of behavior (higher scores indicate more severe behaviors)</td>
</tr>
<tr>
<td>NI-ADL</td>
<td>Nurse Informant – Activities of Daily Living</td>
<td>58-point scale of activities of daily living (higher scores indicate higher level of impairment)</td>
</tr>
<tr>
<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
<td>144-point scale of neuropsychiatric symptoms (higher scores indicate more severe symptoms)</td>
</tr>
<tr>
<td>PGCARS-pos</td>
<td>Philadelphia Geriatric Center Affect Rating Scale - Positive</td>
<td>15-point scale of mood (higher scores indicate more positive affect)</td>
</tr>
<tr>
<td>PGCARS-neg</td>
<td>Philadelphia Geriatric Center Affect Rating Scale - Negative</td>
<td>15-point scale of mood (higher scores indicate more negative affect)</td>
</tr>
<tr>
<td>PGCMS</td>
<td>Philadelphia Geriatric Center Morale Scale</td>
<td>17-point scale of morale (higher scores indicate higher morale)</td>
</tr>
<tr>
<td>SDI</td>
<td>Sleep Disorders Inventory*</td>
<td>84-point scale of sleep-related symptoms (higher scores indicate more severe symptoms)</td>
</tr>
<tr>
<td>SQR</td>
<td>Sleep Quality Rating*</td>
<td>5-point scale in sleep diary of previous night’s sleep quality (1 = very poor night, 5 = outstanding night)</td>
</tr>
</tbody>
</table>

*Non-validated scales developed by investigators specifically for trial by Singer, et al.
IX. References


