ORIGINAL CONTRIBUTION

Effect of Bright Light and Melatonin on Cognitive and Noncognitive Function in Elderly Residents of Group Care Facilities

A Randomized Controlled Trial

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Context Cognitive decline, mood, behavioral and sleep disturbances, and limitations of activities of daily living commonly burden elderly patients with dementia and their caregivers. Circadian rhythm disturbances have been associated with these symptoms.

Objective To determine whether the progression of cognitive and noncognitive symptoms may be ameliorated by individual or combined long-term application of the 2 major synchronizers of the circadian timing system: bright light and melatonin.

Design, Setting, and Participants A long-term, double-blind, placebo-controlled, 2×2 factorial randomized trial performed from 1999 to 2004 with 189 residents of 12 group care facilities in the Netherlands; mean (SD) age, 85.8 (5.5) years; 90% were female and 87% had dementia.

Interventions Random assignment by facility to long-term daily treatment with whole-day bright (±1000 lux) or dim (±300 lux) light and by participant to evening melatonin (2.5 mg) or placebo for a mean (SD) of 15 (12) months (maximum period of 3.5 years).

Main Outcome Measures Standardized scales for cognitive and noncognitive symptoms, limitations of activities of daily living, and adverse effects assessed every 6 months.

Results Light attenuated cognitive deterioration by a mean of 0.9 points (95% confidence interval [CI], 0.04-1.71) on the Mini-Mental State Examination or a relative 5%. Light also ameliorated depressive symptoms by 1.5 points (95% CI, 0.24-2.70) on the Cornell Scale for Depression in Dementia or a relative 19%, and attenuated the increase in functional limitations over time by 1.8 points per year (95% CI, 0.61-2.92) on the nurse-informant activities of daily living scale or a relative 53% difference. Melatonin shortened sleep onset latency by 8.2 minutes (95% CI, 1.08-15.38) or 19% and increased sleep duration by 27 minutes (95% CI, 9-46) or 6%. However, melatonin adversely affected scores on the Philadelphia Geriatric Centre Affect Rating Scale, both for positive affect (–0.5 points; 95% CI, –0.10 to –1.00) and negative affect (0.8 points; 95% CI, 0.20-1.44). Melatonin also increased withdrawn behavior by 1.02 points (95% CI, 0.18-1.86) on the Multi Observational Scale for Elderly Subjects scale, although this effect was not seen if given in combination with light. Combined treatment also attenuated aggressive behavior by 3.9 points (95% CI, 0.88-6.92) on the Cohen-Mansfield Agitation Index or 9%, increased sleep efficiency by 3.5% (95% CI, 0.8%-6.1%), and improved nocturnal restlessness by 1.00 minute per hour each year (95% CI, 0.26-1.78) or 9% (treatment×time effect).

Conclusions Light has a modest benefit in improving some cognitive and noncognitive symptoms of dementia. To counteract the adverse effect of melatonin on mood, it is recommended only in combination with light.

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In elderly patients with dementia, cognitive decline is frequently accompanied by disturbances of mood, behavior, sleep, and activities of daily living,[1-3] which increase caregiver burden and the risk of institutionalization.[4-7] The limited treatment possibilities create an opportunity for other symptom management approaches.[8-11]

Changes in the circadian pacemaker of the brain, located in the hypothalamic suprachiasmatic nucleus, may contribute to cognitive, mood, behavioral, and sleep disturbances.[12-18] The circadian timing system is highly sensitive to environmental light and the hormone melatonin[19] and may not function optimally in the absence of their synchronizing effects. In elderly patients with dementia, synchronization may be attenuated if light exposure and melatonin production are reduced.[20,21] Indeed, bright light ameliorates behavioral[22] and sleep[20] disturbances.

To our knowledge, no previous studies in humans have applied long-term combined stimulation of the circadian timing system with daily light and melatonin. We conducted a multicenter, double-blind, randomized placebo-controlled trial that evaluated the effects of up to 3.5 years of daily supplementation of light and/or melatonin. Using a practical clinical trial approach,[23] long-term treatment effective-

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ness on a broad range of health outcomes including cognitive, mood, behavioral, functional, and sleep disturbances were evaluated in a diverse population typical of care facilities for elderly residents with dementia. We hypothesized that long-term treatment would attenuate cognitive decline and depression, as the primary and secondary outcomes, respectively, and would moreover ameliorate behavioral, functional, and sleep disturbances.

METHODS

Participants and Group Care Facilities

The participants were 189 residents of 12 different Dutch homes for the elderly (170 women and 19 men, which is a rate representative of Dutch homes for the elderly; mean [SD] age, 85.8 [5.5] years) living in assisted care facilities, in which residents have their own apartment where they sleep and retreat, but spend most of the daytime in a common living room supervised by caregivers. The facility is classified as an open type. Residents may need to be transferred to a nursing home if they develop unsolvable behavioral and/or cognitive problems that lead to an unsafe situation; when they wander from the facility; or when physical disabilities cause too much burden for the nursing staff. Of the 61 homes for the elderly that were initially approached, 12 confirmed that they had a group facility with daily occupation and would be willing to participate. For recruitment, all 253 residents living in the facilities were asked for verbal consent and the patients' responsible relatives were asked to provide written informed consent. Consent was obtained from 189. No other inclusion criteria were applied to obtain a sample that is representative of the environment, which is consistent with the design of a practical clinical trial.[23] Exclusion criteria were the use of monoamine oxidase inhibitors, long-term use of nonsteroid antiinflammatory drugs, severe liver or kidney dysfunction, and aphakia. None of the potential participants had to be excluded. The Medical Ethics Committees of Hospital De Gelderse Vallei, Ede, and the VU University Medical Center, Amsterdam, the Netherlands, approved the study.

The clinical diagnosis of dementia was made according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition *(DSM-IV)* criteria for dementia and dementia subtypes.[24] To determine the clinical diagnosis of probable Alzheimer disease, criteria from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) were used.[25] Of the 189 participants, 120 (63%) met the NINCDS-ADRDA criteria for probable Alzheimer disease, 20 (11%) met the *DSM-IV* criteria for vascular dementia, and 24 (13%) met criteria for other types of dementia, including dementia due to multiple etiologies (9 cases), frontal-type dementia (3 cases), Lewy body dementia (2 cases), Parkinson disease (2 cases), Wernicke-Korsakoff (1 case), and dementia not otherwise specified (7 cases). Seventeen participants (8%) did not meet the criteria for dementia, but stayed in the group care facility for various medical or psychosocial reasons. In 8 participants, data on medical history were insufficient to reach a reliable clinical diagnosis.

To investigate possible systematic group differences in the environmental setting of the participants, all facilities were rated on the Therapeutic Environment Screening Scale (TESS).[26,27] The TESS assesses the quality of nursing home environments for residents with dementia and includes items on the general conditions of the environment such as noise, lighting, design, and maintenance, as well as questions about staff interactions with residents and about the involvement of residents in planned activities. The sum score ranges between 0 and 166, with higher scores indicating a supposedly more therapeutic environment. No cutoff scores have been established. In the present study, TESS ratings ranged between 90 and 129. Group means are given in TABLE 1.

Study Design

In a 2×2 factorial design, facilities were randomly assigned using the Microsoft Excel (Redmond, Washington) random number function to 1 of the 2 light conditions and participants to double-blind daily intake of melatonin (2.5 mg, Terafarm, Brielle, the Netherlands, n=95) or placebo (n=94), given approximately 1 hour before bedtime[28] by the nursing staff who ensured adherence. The tablets took about 1 hour to completely dissolve in water, which can be considered a medium-fast release preparation. Timing and dosage were based on previous studies.[28-30]

The 12 homes for the elderly were randomly assigned to active (6 facilities, n=98) or placebo (6 facilities, n=91) light exposure. Forty-nine participants were assigned to light only, 46 to melatonin only, 49 to their combination, and 45 to neither light nor melatonin (double placebo). The mean (SD) ratio of participants assigned to the active melatonin group within each facility was 0.50 (0.06).

Randomization was performed by a research assistant not involved in the study (J. van Heerikhuize, Netherlands Institute for Neuroscience, Amsterdam) and kept concealed. Codes were revealed to the researchers only after completion of the study and subsequent data reduction and processing steps. The flow of the participants included in the study is shown in FIGURE 1.

Light exposure was manipulated by installing a large number of ceiling-mounted fixtures with Plexiglas diffusers containing an equal amount of Philips TLD 840 and 940 fluorescent tubes (Philips Lighting BV, Eindhoven, the Netherlands) in the common living room. Lights were on daily between approximately 9 AM and 6 PM. The aim was an exposure of ±1000 lux, measured before the eyes in the gaze direction. This intensity is technically feasible and has in previous studies been confirmed to synchronize circadian rhythms in healthy people in temporal isolation[31] and to improve circadian activity rhythm disturbances in elderly patients with moderate to severe dementia.[32] For the

placebo group, an equal number of fixtures were installed, but these contained only half of the tubes, accommodated concealed band-stop filters, and were installed at a greater distance from the eyes. The resulting average light exposure measured at eye level in the gaze direction is shown in FIGURE 2. Light intensity was increased to ±1000 lux between 10 AM and 6 PM at the 6 light facilities (active condition) ($P \leq .01$ for all hourly comparisons of the active condition vs baseline except between 3 and 4 PM) while the intensity was not altered at any time of the day for the placebo light facilities (inactive condition). Caregivers were blinded to randomization and were asked to guess their facility's light status. Based on 184 ratings obtained from 89 caregivers over the treatment period, there was no significant difference on a 100-mm illumination pleasantness visual analogue scale (mean [SD] active light condition, 52 [37]; mean [SD] inactive light condition, 55 [34]; 2-tailed *t* test, $P = .47$); neither was there a difference in whether they thought their facility had effective light (active light condition, 69%; inactive light condition, 64%; 2-tailed χ^2 test, $P = .62$).

Procedure

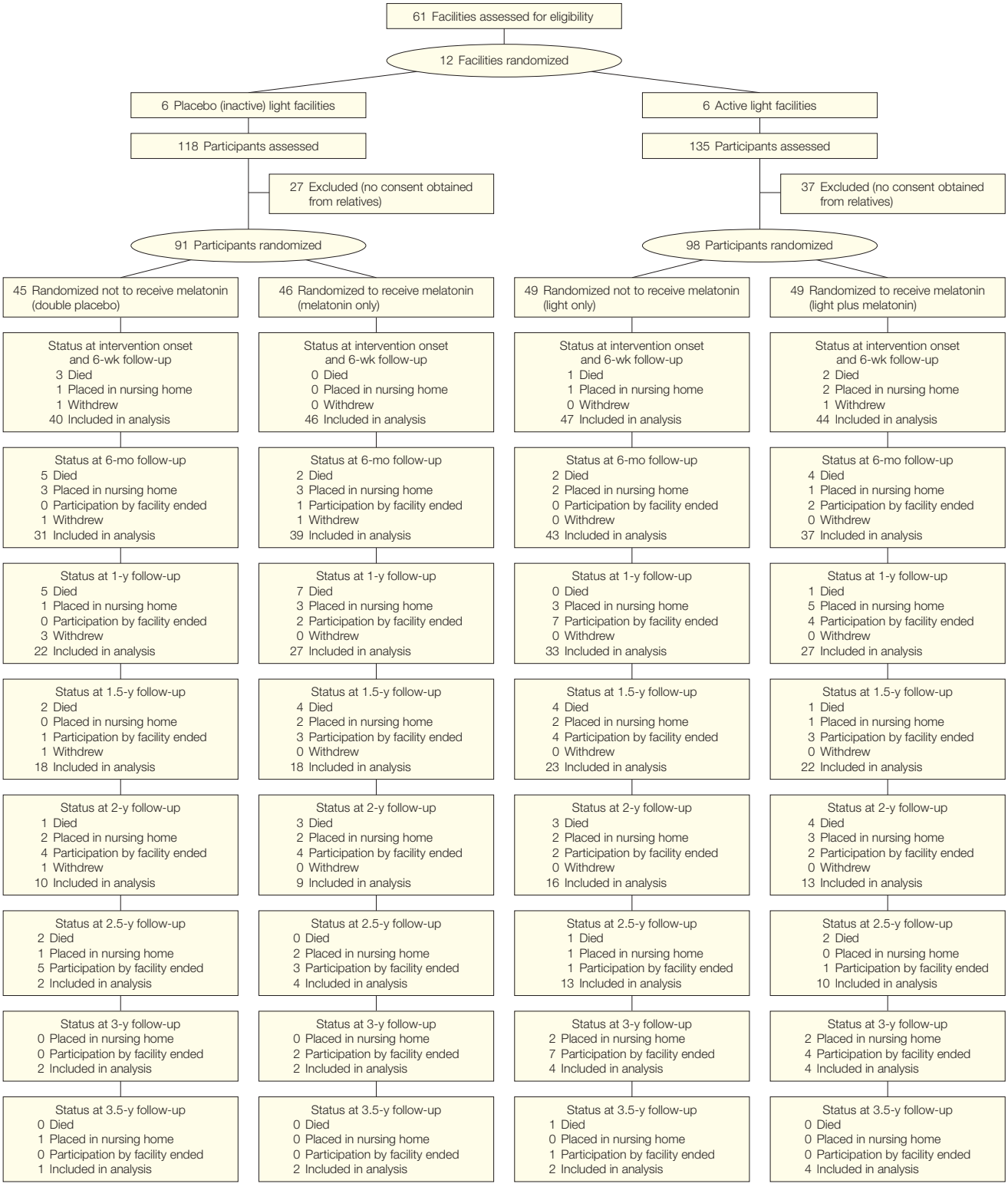
Participants were followed up for up to 3.5 years, a mean (SD) of 15 (12) months. Recruitment and enrollment commenced in 1999 and data acquisition continued until April 14, 2004. Follow-up assessments were made 6 weeks after the start of the treatment, and subsequently every 6 months. Neuropsychiatric symptoms were assessed 6 weeks prior to the start of the treatment in the 129 participants enrolled before the lights were installed. Another 60 participants were enrolled in the study later, and the absence of a baseline assessment in these participants was accounted for by the mixed-effect regression analyses described below. At their first assessment, these 60 participants were similar to those assessed at baseline on the demographic or clinical variables listed in Table 1, except for higher mean (SD) scores on the Mini-Mental State Examination (MMSE) of 18.1 (4.9) vs 14.7 (6.3) (*t* test, $P = .001$),

Table 1. Characteristics of Participants

	6 Placebo (Inactive) Light Facilities		6 Active Light Facilities	
	Double Placebo	Melatonin Only	Light Only	Light + Melatonin
Distribution of Participants Over Groups				
Participants, No./total (%)	45/189 (24)	46/189 (24)	49/189 (26)	49/189 (26)
Female sex, No./total (%)	40/170 (24)	38/170 (22)	45/170 (26)	47/170 (28)
Deceased, No./total (%)	18/60 (30)	16/60 (27)	12/60 (20)	14/60 (23)
Outplaced, No./total (%)	9/48 (19)	12/48 (25)	13/48 (27)	14/48 (29)
Diagnosis, No./total (%)				
Alzheimer disease	22/120 (18)	28/120 (23)	37/120 (31)	33/120 (28)
Other	23/69 (33)	18/69 (26)	12/69 (17)	16/69 (23)
Characteristics Within Groups	**(n = 45)**	**(n = 46)**	**(n = 49)**	**(n = 49)**
Allele, present/participants characterized (%)				
ApoE2	2/19 (11)	4/31 (13)	2/26 (8)	4/27 (15)
ApoE4	5/19 (26)	7/31 (23)	5/26 (19)	6/27 (22)
Age at first assessment, mean (SD), y	85 (5)	86 (5)	85 (6)	87 (6)
Date of first assessment (SD)[a]	May 11 (85 d)	May 12 (85 d)	June 9 (62 d)	June 7 (70 d)
Time followed up, mean (SD), d	381 (343)	433 (324)	550 (389)	443 (393)
TESS score, mean (SD)[b]	104 (9)	104 (8)	101 (10)	102 (12)
Medication use at inclusion and at any follow-up, No. (%)				
Antipsychotics				
Preassessment	11 (24)	12 (26)	18 (37)	13 (27)
During treatment	19 (42)	18 (39)	17 (35)	13 (27)
Anxiolytics				
Preassessment	7 (16)	5 (11)	3 (6)	8 (16)
During treatment	10 (22)	7 (15)	4 (8)	9 (18)
Hypnotics				
Preassessment	10 (22)	11 (14)	11 (22)	13 (27)
During treatment	15 (33)	11 (24)	13 (27)	12 (24)
Antidepressants				
Preassessment	11 (24)	8 (17)	5 (10)	10 (20)
During treatment	13 (29)	8 (17)	9 (18)	10 (20)
Vision, No. (%)				
Lens opacity	17 (38)	10 (22)	10 (20)	17 (35)
Glaucoma	2 (4)	2 (4)	2 (4)	3 (6)

Abbreviation: TESS, Therapeutic Environment Screening Scale.[26,27]
[a] Recruitment and inclusion were staggered so SDs are provided to demonstrate the absence of seasonal differences between the dates of first assessment.
[b] Applied to rate the overall quality of the group care facilities.

Figure 1. Flow of Participants Included in the Study



All available data for participants that were lost to follow-up at any stage were included in the mixed-effect regression analyses.

Multi Observational Scale for Elderly Subjects (MOSES) withdrawn behavior subscale of 19.7 (5.9) vs 16.6 (5.8) (*t* test, *P*=.001), and Cohen-Mansfield Agitation Index (CMAI) of 47.4 (16.2) vs 42.0 (13.5) (*t* test, *P*=.02). Follow-up was primarily determined by the duration of participation of the facility, some of which ended due to logistical reasons including renovations, moving, and staff limitations. Participation of facilities varied between 3.5 years (4 facilities), 3 years (1 facility), 2.5 years (2 facilities), 2 years (2 facilities), 1.5 years (2 facilities), and 0.5 years (1 facility). Secondarily, a major number of participants were lost to follow-up assessment due to death or outplacement to a nursing home, which is inherent to the study population.

Assessment of Outcome Measures

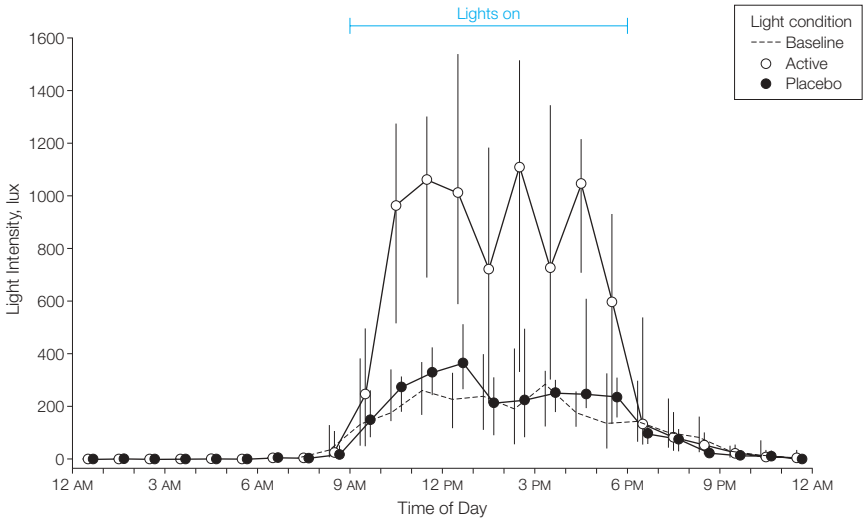
As advocated for practical clinical trials,[23] a broad range of measurements were obtained, including scales for cognitive and noncognitive symptoms and functional abilities as well as sleep-quality estimates derived from actigraphic activity measurement. The ranges and normative cutoff scores (when available) for all scales are provided in TABLE 2. All individuals performing assessments were blinded to treatment allocation.

Three scales were administered by a trained neuropsychologist. The primary outcome, cognitive performance, was assessed with the MMSE.[33] Mood was determined using the Cornell Scale for Depression in Dementia (CSDD), which combines interviews of the patients and caregivers.[34,35] Self-esteem was obtained with the Philadelphia Geriatric Centre Morale Scale (PGCMS).[36,37]

Six scales were completed by the daily caregivers. The Philadelphia Geriatric Centre Affect Rating Scale (PGCARS) rates behavioral expressions of negative and positive mood.[38] Withdrawn behavior was assessed with a subscale of the MOSES.[39] The questionnaire format of the Neuropsychiatric Inventory (NPI-Q) was used to rate the severity and its resulting distress of 12 psychopathological behaviors.[40,41] The CMAI was used to rate agitated behaviors.[42,43] Limitations of activities of daily living were rated on the nurse-informant adaptation[44] (NI-ADL) of the scale by Katz et al.[45] Finally, caregivers rated 16 items on possible adverse effects suggested from previous studies on light or melatonin treatment on a 4-point scale (0=absent, 1=probably absent, 2=probably present, 3=present).

Actigraphy, the continuous assessment of activity with a small wrist-worn recorder, has been recommended as the technique of choice for studying sleep in patients with dementia because poor adherence and diffuse slowing on the electroencephalogram make sleep assessment with standard polysomnographic assessment difficult.[46] Estimates of sleep were obtained from a mean (SD) of 14 (4) days of actigraphic recording using the Actiwatch and accompanying software[47] (Cambridge Neurotechnology, Cambridge, England). Although actigraphy does not discriminate well between wakefulness without movement and sleep, reasonable estimates of sleep parameters can be obtained from long-term recordings.[48] Bedtime and wake time, which are required for sleep estimates, were provided by the nursing staff. The calculated variables quantify 2 processes of sleep: (1) the quantity of sleep and wakefulness, expressed as the duration, onset latency, and efficiency (percentage of time asleep while in bed) of sleep, and nocturnal restlessness (minutes per hour containing any activity during the most restful 5-hour period of the average 24-hour pattern)[49]; (2) the within-sleep structure, expressed as the average durations of nocturnal awakenings and of uninterrupted periods of sleep. Longer periods of activity are more disruptive to sleep while prolonged periods without activity are associated with polysomnographically determined deeper sleep.[50]

Figure 2. Median 24-Hour Light Exposure



Illumination levels were obtained at eye level in the direction of gaze, which was usually slightly downward or at best representing light falling on the vertical plane. Such illumination levels are considerably lower than assessments representing light falling on the horizontal plane directed toward the light sources, but better represent light levels that can enter the eye. Daytime assessments include occasional observations made if participants were not actually present in the common living room where the lights were installed but in their own bedroom. The data thus represent the adherence to the light treatment condition. In the active light condition, the hourly averages between 10 AM and 6 PM were significantly higher compared with pretreatment assessments ($P \leq .01$ for all hourly comparisons of the active condition vs pretreatment assessments; except between 3 and 4 PM, $P=.06$). At no time of day was the intensity increased in the placebo group relative to the pretreatment assessments. Comparisons were made using mixed-effect analysis of 3017 light measurements from 189 participants in 12 facilities assessed repeatedly during the 3.5 years. As long as participants were included in the study, they each contributed to light measurements several times a day and at several follow-up periods. Error bars indicate interquartile range.

Table 2. Assessment Scales Up to 2 Years of Follow-up[a]

Assessment Scale[b]	Total No. of Valid Observations	No. of Follow-up Assessments	No. of Individuals[c]	Treatment Group	Preassessment, Mean (SD) (n = 129)	Follow-up, Mean (SD) 6 wk (n = 177)	6 mo (n = 150)	1 y (n = 109)	1.5 y (n = 81)	2 y (n = 48)
Cognitive Scale										
MMSE (range, 0-30; cutoff, 24)	619	500	174	None[d]	14.3 (7.0)	15.4 (7.3)	15.6 (6.4)	14.5 (5.4)	13.7 (7.4)	12.5 (6.6)
				Light	14.5 (6.2)	16.6 (5.5)	15.6 (5.2)	16.2 (4.5)	17.4 (3.7)	16.1 (4.5)
				Melatonin	15.3 (5.3)	17.1 (6.2)	15.0 (6.3)	16.5 (6.6)	15.1 (6.1)	15.3 (6.0)
				L + M	14.7 (6.8)	15.5 (6.4)	16.5 (6.2)	15.6 (6.1)	15.1 (6.8)	17.8 (4.4)
Mood Scales										
CSDD (range, 38-0; cutoff, 8 minor and 12 major)	730	606	187	None[d]	7.6 (5.1)	7.8 (5.2)	9.3 (6.1)	11.3 (7.4)	12.0 (7.5)	15.1 (8.6)
				Light	7.4 (6.9)	5.8 (4.9)	7.9 (5.6)	11.0 (7.7)	9.9 (5.9)	10.7 (7.3)
				Melatonin	7.0 (5.5)	7.5 (6.2)	8.1 (6.5)	9.6 (7.9)	11.3 (7.6)	10.1 (8.0)
				L + M	7.8 (5.4)	6.8 (5.0)	6.6 (5.0)	8.9 (7.6)	9.7 (6.9)	9.7 (5.4)
PGCARS positive (range, 0-15)	699	576	182	None[d]	10.9 (3.3)	11.3 (2.4)	10.5 (2.6)	11.9 (2.6)	10.6 (2.9)	11.0 (1.0)
				Light	11.0 (3.5)	10.7 (3.5)	10.9 (3.2)	11.6 (3.1)	11.5 (2.2)	11.5 (2.4)
				Melatonin	10.7 (3.0)	10.3 (2.5)	10.3 (2.6)	10.3 (2.9)	10.4 (3.2)	10.8 (3.5)
				L + M	10.9 (3.6)	11.0 (3.0)	11.2 (3.0)	12.2 (3.0)	10.8 (2.8)	11.5 (2.7)
PGCARS negative (range, 15-0)	699	576	182	None[d]	6.2 (3.2)	7.0 (2.9)	6.7 (2.6)	6.2 (2.0)	6.6 (2.2)	9.1 (2.5)
				Light	5.9 (2.3)	5.8 (2.3)	6.1 (2.6)	7.3 (3.2)	6.3 (3.1)	6.4 (2.9)
				Melatonin	6.6 (3.2)	6.5 (2.5)	7.0 (2.8)	7.5 (2.8)	7.2 (3.0)	6.8 (3.3)
				L + M	5.4 (2.5)	6.2 (2.7)	5.5 (2.3)	5.8 (2.7)	6.4 (3.1)	4.6 (1.6)
PGCMS (range, 0-17)	604	492	172	None[d]	10.6 (4.8)	10.4 (4.9)	11.1 (6.0)	11.3 (6.0)	12.0 (4.4)	11.0 (5.6)
				Light	11.9 (4.4)	12.5 (3.7)	13.1 (4.3)	11.3 (3.6)	12.4 (4.1)	11.1 (4.2)
				Melatonin	11.9 (4.5)	11.5 (4.4)	12.9 (4.4)	11.6 (4.8)	10.9 (5.2)	9.3 (5.6)
				L + M	11.7 (4.4)	11.7 (4.1)	12.0 (3.4)	12.0 (4.0)	10.9 (5.3)	12.7 (3.7)
Behavioral Scales										
MOSES (range, 34-0)	701	577	182	None[d]	17.4 (5.2)	16.6 (6.1)	17.9 (6.0)	17.0 (4.1)	19.8 (5.4)	19.9 (5.0)
				Light	19.6 (7.1)	17.5 (5.9)	19.0 (6.1)	17.6 (6.2)	15.5 (4.7)	16.4 (6.2)
				Melatonin	18.9 (6.4)	18.3 (5.9)	20.4 (6.5)	19.2 (6.6)	20.4 (7.0)	17.0 (5.8)
				L + M	18.1 (6.1)	17.6 (5.7)	18.6 (6.4)	17.6 (5.6)	18.5 (5.1)	18.1 (5.9)
NPI-Q severity (range, 36-0)	706	581	183	None[d]	5.2 (5.5)	6.4 (5.3)	5.2 (4.4)	6.1 (3.5)	6.8 (5.0)	8.2 (3.9)
				Light	4.3 (4.4)	4.7 (5.0)	5.7 (5.7)	5.8 (5.7)	4.0 (4.6)	4.9 (5.8)
				Melatonin	5.7 (5.2)	4.8 (4.5)	4.6 (3.8)	5.4 (4.7)	4.5 (4.5)	5.5 (6.7)
				L + M	3.9 (5.0)	4.6 (5.7)	2.7 (3.0)	4.6 (4.5)	4.4 (5.1)	3.7 (4.1)
NPI-Q distress (range, 60-0)	706	581	183	None[d]	4.8 (6.3)	6.0 (5.9)	3.6 (4.6)	3.2 (3.5)	4.2 (4.6)	7.4 (4.5)
				Light	4.8 (5.5)	5.1 (6.0)	6.1 (7.4)	6.0 (7.2)	4.2 (5.3)	5.4 (6.8)
				Melatonin	5.6 (6.8)	4.6 (5.6)	3.8 (4.2)	3.7 (5.2)	2.6 (4.3)	3.6 (5.5)
				L + M	4.4 (6.0)	4.7 (6.5)	2.2 (3.5)	5.5 (6.2)	4.7 (6.6)	3.1 (4.3)
CMAI (range, 203-0)	708	583	184	None[d]	45 (18)	46 (18)	47 (19)	48 (18)	47 (15)	58 (16)
				Light	45 (13)	41 (12)	44 (18)	46 (18)	42 (14)	49 (15)
				Melatonin	48 (17)	45 (15)	47 (19)	48 (16)	49 (19)	44 (19)
				L + M	44 (15)	39 (12)	40 (12)	42 (13)	45 (17)	40 (10)
Functional Limitations Scale										
NI-ADL (range, 58-0)	700	575	181	None[d]	21 (13)	20 (12)	22 (12)	22 (11)	27 (14)	29 (14)
				Light	18 (12)	15 (11)	20 (14)	17 (12)	17 (14)	13 (11)
				Melatonin	23 (11)	22 (14)	23 (13)	27 (14)	31 (16)	28 (15)
				L + M	18 (13)	18 (12)	16 (11)	17 (11)	17 (10)	16 (9)
Actigraphic Sleep Estimates										
Sleep efficiency (range, 0-100),%	566	466	164	None[d]	76 (13)	72 (13)	75 (12)	73 (12)	70 (14)	78 (11)
				Light	70 (16)	73 (11)	72 (12)	74 (11)	76 (10)	74 (12)
				Melatonin	72 (13)	75 (12)	78 (13)	74 (15)	74 (14)	71 (17)
				L + M	73 (11)	75 (12)	78 (8)	77 (11)	78 (11)	80 (6)
Sleep onset latency, min	566	466	164	None[d]	31 (23)	42 (49)	32 (38)	46 (59)	59 (86)	23 (27)
				Light	50 (36)	48 (36)	41 (31)	51 (49)	29 (14)	33 (27)
				Melatonin	54 (61)	37 (31)	28 (26)	40 (32)	37 (31)	41 (49)
				L + M	44 (34)	42 (37)	26 (17)	40 (30)	28 (27)	20 (18)
Total sleep duration, h	566	466	164	None[d]	8.7 (2.1)	8.0 (1.8)	8.1 (1.8)	8.2 (1.7)	8.0 (1.8)	8.0 (2.1)
				Light	7.4 (2.1)	7.6 (1.2)	7.5 (1.2)	7.6 (1.1)	7.9 (1.4)	7.4 (1.2)
				Melatonin	8.3 (1.5)	8.2 (1.6)	9.1 (2.1)	8.6 (2.0)	8.3 (1.7)	8.0 (2.0)
				L + M	7.7 (1.4)	8.3 (1.8)	8.5 (1.4)	8.3 (1.4)	8.5 (1.5)	8.3 (1.3)

(continued)

At each assessment, the prescription of antipsychotics, anxiolytics, hypnotics, and antidepressants was retrieved from the medical record and scored as present or absent. Finally, a physician performed a visual examination focusing on the presence of opacity of the lens and glaucoma.

Statistical Analysis

Mixed-effect regression analysis[51] was used, which is the analysis of choice for realistic long-term data sets in psychiatry and in an elderly long-term care population,[52,53] which typically have variable numbers of observations due to the causes described above. The analyses were performed with the MLwiN software (version 2.0, Institute of Education, London, England) and accounted for the 3-level nested structure of the data set (ie, a variable number of observations nested within participants and participants grouped in 12 facilities). Details are given in the online supplemental information (see http://www.jama.com). Melatonin, light, and their interaction were dummy coded in 3 variables indicating the presence of active treatment at any observation and analyzed in a 2×2 factorial design. Both treatment effects (ie, independent of time) and time × treatment effects (ie, treatment effects changing linearly over time) were evaluated. In addition, the regression models allowed for inclusion of linear changes over time, and for modification of level, time course, and treatment effect by missing data patterns. Logistic mixed-effect regression was applied to evaluate possible group differences and group × time interactions in the prescription of psychotropic medication.

Special attention was given to the fact that (particularly after 1.5 years) many cases were lost to follow-up either due to noninformative reasons (discontinuation of participation by the facility) or to possibly informative causes (death or nursing home transfer). In a predetermined analysis, missing data due to (1) death or nursing home placement and (2) insufficient communicative abilities at any assessment occasion were considered to be informative and dummy coded (indicating presence of this condition for a participant at any point in time) to allow for evaluation of their possible effects in a pattern-mixture model.[54] Second, to obtain the most simple acceptable regression equation insensitive to a reduction in the follow-up time, a post hoc sensitivity analysis was used to verify whether treatment effects obtained from analyses on the complete 3.5-year data set were still present in a reduced data set including only the first 1.5 years of follow-up data. A further preplanned analysis examined possible effect modification by diagnosis by including dummy coding of the Alzheimer disease diagnosis in the regression models. Possible effect modification by opacity of the lens of the eye and glaucoma were likewise examined in a post hoc analysis. The most simple acceptable regression equations were selected using the likelihood ratio χ^2 test.

Significance levels for effects were set at less than .05 with 2-sided testing. Analyses were intention to treat; none of the participants switched treatment and the analyses included all randomized participants. Additional *t* tests, χ^2 tests, and simple logistic regressions were performed using SPSS version 14.0 (SPSS Inc, Chicago, Illinois).

Statistical Power

At the onset of the study it was estimated that participants would remain in the protocol for an average of 2.5

Table 2. Assessment Scales Up to 2 Years of Follow-up[a] (cont)

Assessment Scale[b]	Total No. of Valid Observations	No. of Follow-up Assessments	No. of Individuals[c]	Treatment Group	Preassessment, Mean (SD) (n = 129)	Follow-up, Mean (SD)				
						6 wk (n = 177)	6 mo (n = 150)	1 y (n = 109)	1.5 y (n = 81)	2 y (n = 48)
Actigraphic Sleep Estimates										
Nocturnal restlessness (range, 60-0), min/h	566	466	164	None[d]	11.3 (6.5)	13.2 (7.9)	11.4 (6.3)	12.0 (6.0)	13.7 (7.0)	13.2 (7.2)
				Light	12.9 (9.6)	12.6 (7.4)	12.1 (6.7)	10.5 (6.3)	10.1 (6.1)	10.9 (7.0)
				Melatonin	12.1 (6.1)	11.8 (7.1)	10.4 (6.2)	11.1 (8.1)	11.2 (5.5)	12.5 (6.8)
				L + M	11.8 (5.4)	11.6 (6.4)	10.5 (5.6)	9.6 (5.4)	9.0 (5.4)	9.5 (4.1)
Duration of awakenings, min	566	466	164	None[d]	4.4 (2.5)	4.8 (2.9)	3.8 (1.9)	4.1 (2.1)	3.7 (1.2)	3.5 (1.0)
				Light	5.1 (2.7)	4.1 (1.6)	4.6 (2.0)	4.8 (1.8)	4.5 (1.3)	4.3 (1.8)
				Melatonin	4.3 (1.6)	4.5 (2.2)	4.2 (1.8)	4.2 (1.5)	5.5 (4.0)	4.7 (1.7)
				L + M	4.8 (2.2)	4.1 (1.4)	4.1 (1.9)	4.1 (1.5)	4.1 (1.2)	3.5 (1.1)
Duration of uninterrupted sleep epochs, min	566	466	164	None[d]	33 (38)	21 (15)	21 (13)	35 (67)	17 (10)	20 (9)
				Light	23 (12)	23 (13)	22 (17)	28 (22)	26 (11)	27 (31)
				Melatonin	18 (7)	27 (26)	30 (23)	23 (15)	32 (36)	33 (33)
				L + M	25 (15)	24 (17)	29 (25)	39 (62)	26 (13)	22 (8)

Abbreviations: CMAI, Cohen-Mansfield Agitation Index; CSDD, Cornell Scale for Depression in Dementia; L + M, light plus melatonin; MOSES, Multi Observation Scale for Elderly Subjects; MMSE, Mini-Mental State Examination; NI-ADL, nurse-informant activities of daily living adaptation[44] of the scale by Katz et al[45]; NPI-Q, questionnaire format of the Neuropsychiatric Inventory; PGCARS, Philadelphia Geriatric Center Affect Rating Scale; PGCMS, Philadelphia Geriatric Center Morale Scale.

[a] The number of observations during the last 1.5 years were limited and therefore data are only shown up to 2 years of follow-up. Group averages for the cognition ratings appear to increase over the follow-up assessments. This does not actually reflect within-participant changes, but rather the change in group size at each subsequent follow-up. First, participants who dropped out had worse cognitive ratings. Second, 60 participants enrolled in the study after lights had already been installed. At their first assessment, these 60 participants had higher scores on the MMSE.

[b] Range is shown as worst to best.

[c] For example, the neuropsychologist obtained a total of 619 successful MMSE assessments, of which 500 were follow-up assessments, for 174 participants. In addition to failure of observation reported in the "Results" section, a few observations were missed for some variables due to issues of ambiguity or readability in the rating reports.

[d] Indicates double placebo.

years, allowing for 6 follow-up assessments (1 short-term and 5 half yearly). Under the assumption of a within-subject correlation of $r=0.50$ and using the formulas provided by Twisk,[51] 147 participants would be needed to attain, at a 2-sided a level of less than .05, a power of 0.80 to detect effect sizes of 0.25 for main effects and 0.35 for interactions (ie, between the conventional definition of a small effect size of 0.20 to a moderate effect size of 0.50). Because new inhabitants, assigned to the special care facilities after study initiation, were faced with the presence of the dedicated lighting systems, they were allowed to participate, yielding a total of 189 participants. A post hoc power analysis, taking into account the reduced follow-up and larger sample size than anticipated (189 participants followed-up for 3.25 assessments on average), yielded minimal detectable effect sizes of 0.23 for main effects and 0.33 for interactions.

RESULTS

Randomization was balanced in that none of the individual or environmental characteristics, use of medication, or pretreatment outcome variable levels differed significantly between the 4 groups (Table 1; all $P>.05$, average $P=.59$; χ^2 tests performed for frequencies and analyses of variance for levels). The participants included in the study and followed up in the 4 groups are shown in Figure 1. An overview of the number of observations and the subgroup means and standard deviations through 2 years are shown in Table 2. Treatment effects analyzed, taking into account the factorial design, are given in TABLE 3.

Cognition

Of the maximum number of possible MMSE observations, 15% (112/744) failed due to insufficient communication abilities and 1% (6/744) due to absence of the participants during the neuropsychologist visit. Regression analysis showed that light ameliorated cognitive decline overall by 0.9 points (95% confidence interval [CI], 0.04-1.71, $P=.04$) on the MMSE or a relative 5% (all percentages given relative to intercept unless stated otherwise). The effect was best described as a fixed difference at all time points, and thus left the rate of progressive worsening unchanged.

Mood Scales

Of the maximum number of possible CSDD depression observations, 2% (14/744) were missing due to absence of the participant or a knowledgeable caregiver during the neuropsychologist visit. Light treatment ameliorated depressive symptoms by 1.5 points (95% CI, 0.24-2.70; $P=.02$) on the CSDD or a relative 19%. Of the maximum number of PGCMS scores on the participants' self-esteem, 18% (134/744) failed due to insufficient communication abilities and 1% (6/744) failed due to absence of the participant during the neuropsychologist visit. No treatment effect was found for the PGCMS ($P=.18$ for light, $P=.36$ for melatonin, and $P=.28$ for light plus melatonin). Of the maximum possible number of caregiver ratings on the PGCARS, MOSES, NPI-Q, CMAI, and NI-ADL, 4% (30/744) failed because caregivers stated that they were unable to provide a rating due to limitations of communication, abilities, or observability of the participants and 1% (7/744) due to incomplete data. Melatonin adversely affected observed mood by lowering positive mood ratings by 0.5 points (95% CI, 0.10-1.00; $P=.02$) on the PGCARS positive or 5% and increasing negative mood rating by 0.8 points (95% CI, 0.20-1.44; $P=.01$) on the PGCARS negative or 14%. A light × melatonin interaction effect of –1.00 point (95% CI, –0.17 to –1.82; $P=.02$) on the PGCARS negative or 17% indicated that the adverse effect of melatonin on negative mood expressions was compensated for in those participants who received bright light in addition to melatonin.

Behavioral Scales

Melatonin treatment aggravated the withdrawn behavior rating by 1.02 points (95% CI, 0.18-1.86; $P=.02$) on the MOSES or 7%. No treatment effect was found for the NPI-Q severity ($P=.41$ for light, $P=.52$ for melatonin, and $P=.77$ for light plus melatonin) and caregiver distress ($P=.18$ for light, $P=.32$ for melatonin, and $P=.80$ for light plus melatonin). Combined light and melatonin treatment ameliorated agitated behavior by 3.9 points (95% CI, 0.88-6.92; $P=.01$) on the CMAI or a relative 9%.

Activities of Daily Living

Light treatment attenuated the gradual increase in functional limitations by 1.8 points (95% CI, 0.61-2.92; $P=.003$) on the NI-ADL per year (ie, a relative 53% less steep increase compared with the increase of 3.3 points per year in participants in the inactive light condition).

Sleep

Of the maximum number of possible actigraphic recordings, 22% (160/744) failed due to nonadherence and 2% (14/744) due to logistics. The percentage of missing data did not vary across time points ($\chi^2_8=5.4$, $P=.71$). Light and melatonin treatment affected sleep in several ways. As to the quantity of sleep and wakefulness, the 4 variables obtained were all affected by the treatments. An important variable is nocturnal restlessness, quantified as the minutes per hour containing any activity during the most restful 5-hour period of the average activity profile. Combined treatment (light and melatonin) ameliorated nocturnal restlessness with an effect that increased over time, ie, by 1.00 minute per hour each year (95% CI, 0.26-1.78; $P=.01$) or 9%. Combined treatment also increased sleep efficiency by 3.5% (95% CI, 0.8%-6.1%; $P=.01$). Melatonin shortened sleep onset latency by 8.2 minutes (95% CI, 1.08-15.38; $P=.02$) or a relative 19% overall. Sleep duration increased by 27 minutes (95% CI, 9-46; $P=.004$) or 6% with melatonin treatment and in addition by 10 minutes per year (95% CI, 0.4-20; $P=.04$) with light treatment or 2%.

Regarding sleep structure, the treatments significantly reduced sleep fragmentation. The combination of light

Table 3. Treatment Effect Estimates[a]

						Pattern-Mixture Analysis[c]			
		Overall Analysis Up to 3.5-y Follow-up		Sensitivity Analysis for Up to 1.5-y Follow-up[b]		Effect Modification by Drop Out		Effect Modification by Insufficient Communicative Abilities	
Assessment Scale	Treatment Effect	Effect Estimate (95% CI)	*P* Value	Effect Estimate (95% CI)	*P* Value	Effect Estimate (95% CI)	*P* Value	Effect Estimate (95% CI)	*P* Value
Cognitive Scale									
Mini-Mental State Examination	Light	0.87 (0.04 to 1.71)	.04	1.03 (0.18 to 1.87)	.02	1.45 (–0.14 to 3.03)	.07	–0.27 (–1.77 to 1.23)	.72
	Melatonin	–0.01 (–0.79 to 0.76)	.97	–0.14 (–0.91 to 0.64)	.73				
	L × M	–0.23 (–1.38 to 0.93)	.70	–0.49 (–1.64 to 0.66)	.40				
Mood Scales									
Cornell Scale for Depression in Dementia	Light	–1.47 (–2.70 to –0.24)	.02	–1.76 (–2.98 to –0.53)	.01	1.10 (–0.91 to 3.11)	.28	–0.02 (–2.05 to 2.01)	.98
	Melatonin	–0.82 (–1.87 to 0.23)	.12	–0.73 (–1.79 to 0.33)	.18				
	L × M	–0.94 (–2.48 to 0.61)	.24	–1.01 (–2.56 to 0.54)	.20				
Philadelphia Geriatric Center Affect Rating Scale positive	Light	–0.17 (–0.81 to 0.48)	.61	–0.21 (–0.86 to 0.45)	.54				
	Melatonin	–0.55 (–1.00 to –0.10)	.02	–0.50 (–0.97 to –0.03)	.04	–0.14 (–1.04 to 0.77)	.76	0.14 (–0.81 to 1.08)	.78
	L × M	0.60 (–0.28 to 1.49)	.18	0.57 (–0.35 to 1.48)	.23				
Philadelphia Geriatric Center Affect Rating Scale negative	Light	0.50 (–0.07 to 1.07)	.08	0.38 (–0.19 to 0.94)	.19				
	Melatonin	0.82 (0.20 to 1.44)	.01	0.82 (0.20 to 1.45)	.01	–0.55 (–1.73 to 0.63)	.36	0.24 (–0.95 to 1.44)	.69
	L × M	–1.00 (–1.82 to –0.17)	.02	–0.94 (–1.78 to –0.09)	.03	1.07 (–0.44 to 2.57)	.16	–0.43 (–2.00 to 1.14)	.59
Philadelphia Geriatric Center Morale Scale	Light	0.35 (–0.28 to 0.98)	.18	0.49 (–0.16 to 1.14)	.18				
	Melatonin	0.21 (–0.38 to 0.80)	.36	0.25 (–0.36 to 0.86)	.36				
	L × M	0.07 (–0.71 to 0.85)	.28	0.09 (–0.71 to 0.89)	.28				
Behavioral Scales									
Multi Observation Scale for Elderly Subjects	Light	–0.51 (–1.55 to 0.53)	.34	–0.68 (–1.76 to 0.40)	.22				
	Melatonin	1.02 (0.18 to 1.86)	.02	0.81 (–0.07 to 1.69)	.07	0.35 (–1.29 to 1.98)	.68	0.80 (–0.88 to 2.48)	.35
	L × M	–0.74 (–2.35 to 0.87)	.37	–0.82 (–2.45 to 0.81)	.32				
Neuropsychiatric Inventory questionnaire format on severity	Light	0.23 (–0.73 to 1.19)	.41	0.06 (–0.92 to 1.04)	.90				
	Melatonin	–0.41 (–1.21 to 0.39)	.52	–0.54 (–1.36 to 0.28)	.20				
	L × M	–0.36 (–1.42 to 0.70)	.77	–0.42 (–1.50 to 0.66)	.45				
Neuropsychiatric Inventory questionnaire format on distress	Light	0.25 (–0.87 to 1.37)	.18	0.11 (–1.04 to 1.25)	.85				
	Melatonin	–0.68 (–1.64 to 0.28)	.32	–0.72 (–1.71 to 0.26)	.15				
	L × M	–0.56 (–1.81 to 0.69)	.80	–0.54 (–1.84 to 0.76)	.41				
Cohen-Mansfield Agitation Index	Light	–1.61 (–4.82 to 1.60)	.33	–1.85 (–5.04 to 1.34)	.26				
	Melatonin	1.28 (–1.99 to 4.55)	.44	1.40 (–1.89 to 4.68)	.41				
	L × M	–3.90 (–6.92 to –0.88)	.01	–3.83 (–6.90 to –0.75)	.01	–5.35 (–11.19 to 0.49)	.07	–0.51 (–6.64 to 5.61)	.87

(continued)

and melatonin treatment interacted to reduce the average duration of individual brief nocturnal awakenings by 0.5 minutes per year (95% CI, 0.21-0.85; $P=.01$) or a relative 12%. Melatonin treatment increased the average duration of uninterrupted periods of sleep by 5.8 minutes (95% CI, 1.0-10.6; $P=.02$) or a relative 25%.

Table 3. Treatment Effect Estimates[a] (cont)

		Overall Analysis Up to 3.5-y Follow-up		Sensitivity Analysis for Up to 1.5-y Follow-up[b]		Pattern-Mixture Analysis[c]: Effect Modification by Drop Out		Pattern-Mixture Analysis[c]: Effect Modification by Insufficient Communicative Abilities	
Assessment Scale	Treatment Effect	Effect Estimate (95% CI)	*P* Value	Effect Estimate (95% CI)	*P* Value	Effect Estimate (95% CI)	*P* Value	Effect Estimate (95% CI)	*P* Value
Functional Scale									
Nurse-informant activities of daily living scale[44,45]	Light	–1.77/y (–2.92 to –0.61)	.003	–2.02/y (–3.78 to –0.26)	.02	–0.26 (–2.72 to 2.21)	.84	0.04 (–1.39 to 1.48)	.95
	Melatonin	–0.92 (–2.33 to 0.49)	.20	–1.52 (–3.00 to –0.04)	.04				
	L × M	–1.25 (–3.13 to 0.63)	.19	–1.73 (–3.70 to 0.23)	.08				
Actigraphic Sleep Estimates									
Sleep efficiency, %	Light	0.83 (–1.89 to 3.55)	.55	1.00 (–1.77 to 3.78)	.48				
	Melatonin	1.50 (–1.40 to 4.40)	.31	1.72 (–1.18 to 4.62)	.25				
	L × M	3.46 (0.84 to 6.09)	.01	2.92 (0.25 to 5.58)	.03	1.66 (–3.49 to 6.81)	.53	–0.55 (–7.47 to 6.38)	.88
Sleep onset latency, min	Light	–3.61 (–11.23 to 4.01)	.35	–2.46 (–10.38 to 5.45)	.54				
	Melatonin	–8.23 (–15.38 to –1.08)	.02	–7.16 (–14.56 to 0.23)	.06	1.33 (–13.05 to 15.72)	.86	1.54 (–15.60 to 18.67)	.86
	L × M	–1.71 (–14.3 to 10.8)	.79	0.29 (–12.7 to 13.3)	.97				
Total sleep duration, min	Light	10.14/y (0.38 to 19.90)	.04	15.66/y (2.14 to 29.18)	.02	0.05 (–0.24 to 0.34)	.75	0.15 (–0.14 to 0.44)	.31
	Melatonin	27.48 (8.55 to 46.41)	.004	20.28 (4.05 to 36.51)	.01	0.14 (–0.39 to 0.66)	.61	–0.13 (–0.76 to 0.51)	.70
	L × M	8.46 (–27.6 to 44.6)	.65	8.64 (–22.8 to 40.0)	.59				
Nocturnal restlessness, min/h	Light	–0.25 (–1.47 to 0.97)	.69	–0.17 (–1.44 to 1.10)	.79				
	Melatonin	–0.48 (–1.62 to 0.66)	.41	–0.40 (–1.60 to 0.79)	.51				
	L × M	–1.00 (–1.78 to –0.26)	.01	–1.39 (–2.62 to –0.17)	.03	–0.54 (–2.17 to 1.09)	.52	0.26 (–2.26 to 2.77)	.84
Duration of awakenings, min	Light	–0.50 (–1.04 to 0.04)	.07	–0.57 (–1.15 to 0.02)	.06				
	Melatonin	–0.05 (–0.52 to 0.41)	.83	–0.02 (–0.52 to 0.49)	.95				
	L × M	–0.53/y (–0.85 to –0.21)	.01	–0.63/y (–1.21 to –0.05)	.03	–0.20 (–0.89 to 0.50)	.58	–1.00 (–2.16 to 0.16)	.09
Duration uninterrupted sleep epochs, min	Light	0.05 (–4.93 to 5.03)	.98	0.29 (–5.07 to 5.66)	.91				
	Melatonin	5.83 (1.05 to 10.61)	.02	6.03 (0.96 to 11.09)	.02	2.02 (–7.56 to 11.60)	.68	–7.71 (–18.98 to 3.56)	.18
	L × M	–0.15 (–8.30 to 8.00)	.97	0.50 (–8.16 to 9.15)	.91				

Abbreviations: CI, confidence interval; L × M, light × melatonin interaction.

[a] Obtained from analyses using all available data assessed during up to 3.5 years of follow-up. The estimates indicate factorial effects; for example, light treatment increased MMSE scores by 0.87 points (95% CI, 0.04-1.71), irrespective of whether participants were assigned to the active or placebo melatonin condition. Effect estimates were obtained from intent-to-treat mixed-effect regression analyses including a pattern-mixture model approach[56] to account for missing data. Treatment effects were best modeled as modulated by time for the effect of light on the NI-ADL, and for the effect of the combination of light and melatonin on nocturnal restlessness and the mean duration of intermittent awakenings (expressed in units of effect per year).

[b] Because, after 1.5 years of follow-up, only a limited number of observations could be obtained, a sensitivity analysis was performed to estimate effects as obtained from analysis on a data set that was limited to the first 1.5 years of follow-up.

[c] Missing data due to (1) death or nursing home placement and (2) insufficient communicative abilities at any assessment occasion were considered to be informative and dummy coded (indicating presence of this condition for a participant at any point in time) to allow for evaluation of their possible effects in a pattern mixture model.[56] None of the treatment × dropout pattern effect estimates reached significance, indicating that treatment effects that reached significance in the overall analyses were not a result of confounding by selective missing data and were of equal size for participants with and without missing data.

Prescription of Medication

The 4 groups did not differ in the proportion of participants receiving psychotropic medication at the onset of their participation (Table 1, all $P > .32$ by χ^2 test). Logistic mixed-effect regression analysis showed that the prescription use of antipsychotics, anxiolytics, hypnotics, and antidepressants did not change after treatment onset compared with prescription use prior to treatment onset (all $P > .80$). There were no effects on prescription use with either light or melatonin treatment or their interaction (all $P > .35$).

Missing Data and Effect Modification by Diagnosis and Visual Impairment

Because, particularly after 1.5 years, many cases were lost to follow-up, it was important to determine whether treatment effects obtained from analyses on the complete 3.5-year data set were present when only the first 1.5 years of follow-up were included in the analysis. Compared with the treatment effect estimates based on all available data, only marginal changes occurred when the estimates were derived from only the first 1.5 years of follow-up (Table 3). In fact, positive treatment effect size estimates were similar or increased when based on the first 1.5 years compared with the full data set. Adverse treatment effect sizes were generally less or unchanged. This sensitivity analysis suggests that the results cannot be attributed to confounding by drop out.

The second approach to assess the impact of dropouts was to code missing data due to (1) death or nursing home placement or (2) insufficient communication abilities in 2 dummy variables to allow for inclusion in the regression analysis according to a pattern-mixture model approach. Individuals who dropped out of the study due to nursing home placement or death scored markedly worse on the MMSE (–3.5; 95% CI, –5.1 to –1.8), PGARS positive (–0.9; 95% CI, –1.5 to –0.4), PGARS negative (0.9; 95% CI, 0.3 to 1.5), MOSES (4.4; 95% CI, 2.9 to 5.8), and NI-ADL (5.5; 95% CI, 2.3 to 8.8). Relative to the decline participants showed overall (all of the following expressed in scale points per year) on the MMSE (–1.1; 95% CI, –1.4 to –0.7), CSDD (2.1; 95% CI, 1.5 to 2.6), MOSES (1.1; 95% CI, 0.8 to 1.5), CMAI (1.3; 95% CI, 0.2 to 2.5), and NI-ADL (3.3; 95% CI, 2.3 to 4.3), participants who dropped out worsened at a faster rate on the MMSE (–1.5; 95% CI, –2.1 to –0.9), CSDD (1.5; 95% CI, 0.6 to 2.4), NPI-Q severity (2.1; 95% CI, 1.3 to 2.9), NPI-Q distress (2.5; 95% CI, 1.5 to 3.5), CMAI (4.2; 95% CI, 2.2 to 6.2), and NI-ADL (2.9; 95% CI, 1.6 to 4.2). Therefore, a pattern-mixture analysis was performed that considered dropouts as informative for the outcome measures. These analyses showed that none of the treatment × drop out or treatment × insufficient communicative abilities interaction terms reached significance when added to the regression models of the outcomes that showed significant treatment effects in the overall analysis (Table 3). Moreover, treatment groups did not differ with regard to the frequency of participants with dropout pattern 1 ($P > .99$) or 2 ($P = .51$) (χ^2 test). Finally, none of the treatment effects was modulated by the presence or absence of the diagnosis of probable Alzheimer disease or by visual impairment (data available on request). Attenuations of the favorable treatment effects on nocturnal restlessness ($P = .07$) and on the mean duration of intermittent awakenings ($P = .08$) for participants with opacity of 1 or both lenses of the eye were the closest to significance.

Adverse Effects

An overview of the average ratings prior to and during treatment is given in TABLE 4. Items with the highest overall ratings were drowsiness and irritability. Of note, in contrast to previous studies on light and melatonin that suggested an increased occurrence of complaints, an increased occurrence by either light or melatonin treatment or their interaction was not found. On the contrary, compared with the pretreatment assessment and the placebo-treated participants, light treatment significantly reduced the ratings on irritability, dizziness, headache, constipation, and inability to sleep. Melatonin reduced the ratings on constipation. No severe adverse events were reported by the patients' physicians. In the only case reported by others, the daughter of a 90-year-old participant diagnosed with probable Lewy body dementia suspected her mother's increase in restlessness and falls to be related to the treatment and requested discontinuation. This patient had been assigned to the double placebo group.

COMMENT

This, to our knowledge, is the first double-blind, placebo-controlled randomized trial evaluating a combination of the circadian stimuli light and melatonin on a daily basis for an average of 15 months. The application of indirect ceiling-mounted, whole-day bright light resulted in optimal adherence and allowed for a verifiable placebo group.

Light reduced the cognitive deficits by 5% without decelerating the progressive cognitive worsening (as is also the case for acetylcholinesterase inhibitors[8]). Light also reduced depressive symptoms by a relative 19% and attenuated the gradual increase in functional limitations by 53%. A similar increase in efficacy over time by 2% was found for its effect on sleep duration.

Melatonin had no effect on the CSDD depression ratings but adversely affected caregiver ratings of withdrawn behavior and mood expressions. We suspect that the long-term daily application of 2.5 mg of melatonin may have induced supraphysiological daytime levels, which are associated with sleepiness and dysphoria.[55,56] Bright light ameliorated the adverse effect on mood. For practical application in elderly residents, a dose lower than 2.5 mg should be considered as well as simultaneous application of bright light.

However, melatonin also induced positive effects. In combination with bright light, it attenuated agitated behavior by 9%. Most notably, melatonin reduced sleep onset latency by a relative 19%, increased total sleep duration by 6%, and increased the mean duration of uninterrupted sleep periods, which has been related to the depth of sleep,[50] by 25%. Furthermore, in combination with bright light, melatonin improved sleep efficiency (3.5%), nocturnal restlessness (9% per year), and the

average duration of brief nocturnal awakenings (12% per year). The strength of the latter 2 effects increased over time with treatment. If effects were sustained over time, prolonged combined treatment could help maintain sleep efficiency above 85%, which has been regarded as a cutoff for clinically relevant disturbed sleep.[57] Our novel finding that some melatonin effects develop slowly and/or only in combination with light treatment may explain the lack of effects in some of the previous short-term studies.[29,58]

Four limitations should be discussed. First, the study was performed in a somewhat heterogeneous group of elderly people, most of whom had dementia, representative of residents in group care facilities. Our trial should therefore be considered a practical clinical trial, which includes a more diverse study population than is usually the case in clinical trials with restricted eligibility criteria. Practical clinical trials have been recommended to provide health care decision makers with a more reliable estimate of applicability.[23] Second, intrinsic to the aim of a practical clinical trial, one should be cautious regarding the multiplicity of analyses and outcomes. However, light consistently improved several important clinical parameters. As noted by Caspi et al,[59] the consistency of results in several parameters suggests a robust finding because the number of significant effects far exceeds the proportion that could be explained by chance. A third issue concerns the limited number of men participating in the present study. Although representative of care facility occupancy in the Netherlands, which is dominated by women, these results may not be generalizable to men. A fourth limitation was the substantial number of participants eventually lost to follow-up. Drop out was primarily due to logistic limitations (ie, discontinuation of facilities) and secondarily related to the very nature of the population under study, which is at high risk of death and transfer to a nursing home. We verified that the treatment effects were not modulated by dropout pattern and were robust in a sensitivity analysis limiting the data set to the first 1.5 years of follow-up.

Table 4. Evaluation of Potential Adverse Effects[a]

	Rating, Mean (SD)[b]					Light[c]		Melatonin		Light + Melatonin	
Complaint	Preassessment	None	Light	Melatonin	Light + Melatonin	Effect Estimate (95% CI)	*P* Value	Effect Estimate (95% CI)	*P* Value	Effect Estimate (95% CI)	*P* Value
Dizziness	0.94 (1.15)	0.89 (1.16)	0.44 (0.94)	0.73 (0.98)	0.56 (1.00)	–0.37 (–0.55 to –0.19)	<.001	–0.24 (–0.49 to 0.01)	.06	0.31 (–0.06 to 0.69)	.12
Drowsiness	0.98 (1.25)	0.97 (1.22)	0.93 (1.25)	1.12 (1.24)	0.94 (1.26)	–0.01 (–0.31 to 0.29)	.93	0.12 (–0.18 to 0.42)	.42	–0.06 (–0.50 to 0.37)	.77
Eye complaints	0.86 (1.22)	0.65 (0.98)	0.52 (0.93)	0.74 (1.08)	0.65 (1.12)	–0.01 (–0.23 to 0.21)	.91	–0.12 (–0.30 to 0.06)	.19	0.36 (–0.01 to 0.74)	.06
Feebleness	0.69 (1.11)	0.52 (0.97)	0.30 (0.80)	0.73 (1.06)	0.43 (0.95)	–0.17 (–0.38 to 0.04)	.11	–0.02 (–0.26 to 0.22)	.88	0.19 (–0.16 to 0.54)	.29
Headache	0.75 (1.07)	0.60 (0.88)	0.52 (0.97)	0.86 (1.03)	0.55 (1.01)	–0.22 (–0.41 to –0.02)	.03	0.01 (–0.23 to 0.24)	.96	0.03 (–0.32 to 0.37)	.88
Hunger	0.38 (0.84)	0.49 (0.92)	0.22 (0.70)	0.32 (0.77)	0.22 (0.74)	0 (–0.20 to 0.19)	.98	–0.15 (–0.34 to 0.05)	.14	–0.08 (–0.36 to 0.20)	.57
Hyperactivity	0.26 (0.80)	0.50 (0.98)	0.25 (0.70)	0.34 (0.80)	0.16 (0.55)	–0.07 (–0.24 to 0.11)	.46	0.10 (–0.09 to 0.28)	.31	–0.21 (–0.48 to 0.06)	.13
Inability to sleep	0.63 (0.96)	0.94 (1.09)	0.20 (0.60)	0.75 (0.95)	0.32 (0.80)	–0.52 (–0.67 to –0.37)	<.001	–0.02 (–0.24 to 0.21)	.87	0.24 (–0.08 to 0.57)	.14
Irritability	1.07 (1.27)	1.29 (1.22)	0.93 (1.20)	1.00 (1.16)	0.57 (1.07)	–0.34 (–0.57 to –0.11)	.004	–0.12 (–0.41 to 0.16)	.40	–0.16 (–0.58 to 0.26)	.45
Nausea	0.36 (0.86)	0.40 (0.77)	0.27 (0.75)	0.40 (0.80)	0.27 (0.79)	–0.05 (–0.23 to 0.14)	.62	0 (–0.19 to 0.19)	>.99	–0.11 (–0.39 to 0.17)	.45
Constipation	0.84 (1.11)	0.88 (1.09)	0.46 (0.92)	0.67 (0.99)	0.23 (0.67)	–0.33 (–0.54 to –0.11)	.003	–0.17 (–0.33 to 0)	.05	0.10 (–0.23 to 0.43)	.55
Pins and needles	0.24 (0.62)	0.46 (0.77)	0.09 (0.38)	0.23 (0.51)	0.19 (0.66)	–0.10 (–0.25 to 0.04)	.16	–0.14 (–0.28 to 0.01)	.06	0.16 (–0.04 to 0.37)	.12
Stomach ache	0.23 (0.62)	0.26 (0.58)	0.21 (0.66)	0.31 (0.65)	0.11 (0.47)	0.02 (–0.12 to 0.16)	.75	–0.02 (–0.16 to 0.13)	.83	–0.04 (–0.25 to 0.18)	.73
Sweating	0.37 (0.89)	0.48 (0.93)	0.26 (0.79)	0.41 (0.88)	0.18 (0.65)	0.17 (–0.02 to 0.37)	.09	0.01 (–0.20 to 0.21)	.96	–0.07 (–0.36 to 0.23)	.66
Trembling hands	0.37 (0.91)	0.45 (0.92)	0.22 (0.69)	0.56 (1.05)	0.39 (0.92)	–0.05 (–0.25 to 0.14)	.61	0.01 (–0.20 to 0.22)	.92	0.07 (–0.25 to 0.39)	.68
Other complaints	0.48 (1.09)	0.30 (0.85)	0.29 (0.88)	0.41 (0.97)	0.28 (0.86)	–0.05 (–0.27 to 0.18)	.69	–0.02 (–0.23 to 0.19)	.85	0.02 (–0.28 to 0.31)	.91

Abbreviation: CI, confidence interval.
[a]Caregivers provided a total of 694 adverse effects scale ratings, of which 571 were follow-up assessments, for 182 participants.
[b]The 16-item ratings were given on a 4-point scale (0 = absent, 1 = probably absent, 2 = probably present, 3 = present).
[c]Light treatment lowered the ratings on irritability, dizziness, headache, constipation, and inability to sleep; treatment with melatonin lowered the ratings on constipation.

We hypothesize that enhancement of the function of circadian timing system has been involved in the treatment effects. Several previous studies[12-18] suggest an involvement of the circadian timing system in optimal brain function, while other studies[20-22] indicate functional deficits in the circadian timing system at advanced age and in dementia. The long-term supplementation of light as the primary stimuli acting on the suprachiasmatic nucleus may have improved its abilities to synchronize rhythms in for example, hormones, metabolism, and peripheral oscillators, which concertedly contribute to an individual's general functioning. This synchronization may be a slow process, which could account for the gradual increase in some of the effects. For example, even in healthy humans and animals, some studies have shown that it may take months until effects of light or exercise on day-night rhythms become evident (reviewed previously[60]). From a practical point of view, one might imagine the effects of enhanced rhythm synchronization on general well-being as comparable with recovery from detrimental effects of jet lag and disturbed sleep.

A final issue to be discussed is whether the statistically significant findings can be interpreted as clinically relevant. Although effects between 3.5 and 3.9 points on the MMSE have been considered clinically significant,[61] no treatments have come close to this large an effect. A meta-analysis concluded that acetylcholinesterase inhibitors improve cognitive performance by about 0.60 to 1.10 points on the MMSE.[62] Although no direct comparison with our findings can be made because our participants were not all diagnosed with Alzheimer disease and showed more severe cognitive deterioration at onset, the effect by light of 0.87 points (95% CI, 0.04-1.71) on the MMSE is of a comparable magnitude. Unlike acetylcholinesterase inhibitors, it did not manifest adverse effects. Of further importance for the evaluation of clinical relevance is that light also contributed to improvements in mood, behavior, functional limitations, and sleep. Given the CSDD cutoff scores of 8 for minor and 12 for major depression, and the present CSDD scores varying between about 8 and 12 on average in the placebo group, the light treatment-related amelioration by 1.5 points (95% CI, 0.24-2.70) on the CSDD or 19% could change the score from major depression to minor depression, or minor depression to no depression. Although we are not aware of cutoff scores for the behavioral and functional scales, a reduction of 58% in the gradual increase in functional limitations could be clinically relevant. On the other hand, with sleep efficiency varying between about 70% and 76% on average in the placebo group, the improvement of 3.5% by combined treatment is not sufficient to reach the often-used cutoff of 85% to overcome clinically relevant disturbed sleep. On the whole, light treatment could have clinically beneficial effects. We did not assess the cost of light treatment; lights were provided at reduced cost and installation was not changed.

In conclusion, the simple measure of increasing the illumination level in group care facilities ameliorated symptoms of disturbed cognition, mood, behavior, functional abilities, and sleep. Melatonin improved sleep, but its long-term use by elderly individuals can only be recommended in combination with light to suppress adverse effects on mood. The long-term application of whole-day bright light did not have adverse effects, on the contrary, and could be considered for use in care facilities for elderly individuals with dementia.

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REFERENCES

1. Lee HB, Lyketsos CG. Depression in Alzheimer's disease: heterogeneity and related issues. *Biol Psychiatry*. 2003;54(3):353-362.
2. Purandare N, Burns A, Craig S, Faragher B, Scott K. Depressive symptoms in patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 2001;16(10):960-964.
3. González-Salvador T, Lyketsos CG, Baker A, et al. Quality of life in dementia patients in long-term care. *Int J Geriatr Psychiatry*. 2000;15(2):181-189.
4. Donaldson C, Tarrier N, Burns A. Determinants of carer stress in Alzheimer's disease. *Int J Geriatr Psychiatry*. 1998;13(4):248-256.

5. Dorenlot P, Harboun M, Bige V, Henrard JC, Ankri J. Major depression as a risk factor for early institutionalization of dementia patients living in the community. *Int J Geriatr Psychiatry*. 2005;20(5): 471-478.
6. Devanand DP, Jacobs DM, Tang MX, et al. The course of psychopathologic features in mild to moderate Alzheimer disease. *Arch Gen Psychiatry*. 1997; 54(3):257-263.
7. Banerjee S, Murray J, Foley B, Atkins L, Schneider J, Mann A. Predictors of institutionalisation in people with dementia. *J Neurol Neurosurg Psychiatry*. 2003; 74(9):1315-1316.
8. Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet*. 2004;363(9427):2105-2115.
9. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA*. 2005;293(5):596-608.
10. Van Someren EJW. Circadian and sleep disturbances in the elderly. *Exp Gerontol*. 2000;35(9-10): 1229-1237.
11. Salzman C, Wong E, Wright BC. Drug and ECT treatment of depression in the elderly, 1996-2001: a literature review. *Biol Psychiatry*. 2002;52(3):265-284.
12. Fekete M, van Ree JM, Niesink RJ, de Wied D. Disrupting circadian rhythms in rats induces retrograde amnesia. *Physiol Behav*. 1985;34(6):883-887.
13. Cho K. Chronic 'jet lag' produces temporal lobe atrophy and spatial cognitive deficits. *Nat Neurosci*. 2001;4(6):567-568.
14. Walker MP, Stickgold R. Sleep-dependent learning and memory consolidation. *Neuron*. 2004; 44(1):121-133.
15. Swaab DF, Fliers E, Partiman TS. The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. *Brain Res*. 1985;342(1):37-44.
16. Zhou JN, Riemersma RF, Unmehopa UA, et al. Alterations in arginine vasopressin neurons in the suprachiasmatic nucleus in depression. *Arch Gen Psychiatry*. 2001;58(7):655-662.
17. Liu RY, Zhou JN, Hoogendijk WJG, et al. Decreased vasopressin gene expression in the biological clock of Alzheimer's disease patients with and without depression. *J Neuropathol Exp Neurol*. 2000; 59(4):314-322.
18. Moe KE, Vitiello MV, Larsen LH, Prinz PN. Sleep/wake patterns in Alzheimer's disease: relationships with cognition and function. *J Sleep Res*. 1995;4(1): 15-20.
19. Moore RY. Entrainment pathways and the functional organization of the circadian system. *Prog Brain Res*. 1996;111:103-119.
20. Van Someren EJW, Riemersma RF, Swaab DF. Functional plasticity of the circadian timing system in old age: light exposure. *Prog Brain Res*. 2002;138: 205-231.
21. Riemersma RF, Mattheij CAM, Swaab DF, Van Someren EJW. Melatonin rhythms, melatonin supplementation and sleep in old age. In: Straub RH, Mocchegiani E, eds. *The Neuroendocrine Immune Network in Ageing.* Vol 4. Amsterdam, the Netherlands: Elsevier; 2004:195-211.
22. Mishima K, Okawa M, Hishikawa Y, Hozumi S, Hori H, Takahashi K. Morning bright light therapy for sleep and behavior disorders in elderly patients with dementia. *Acta Psychiatr Scand*. 1994;89(1):1-7.
23. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*. 2003; 290(12):1624-1632.
24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.
25. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-944.
26. Sloane PD, Mathew LJ. The Therapeutic Environment Screening Scale. *Am J Alz Care Related Disord Res*. 1990;5(1):22-26.
27. Slaughter S, Calkins M, Eliasziw M, Reimer M. Measuring physical and social environments in nursing homes for people with middle- to late-stage dementia. *J Am Geriatr Soc*. 2006;54(9):1436-1441.
28. Zhdanova IV, Lynch HJ, Wurtman RJ. Melatonin—a sleep-promoting hormone. *Sleep*. 1997;20(10): 899-907.
29. Singer C, Tractenberg RE, Kaye J, et al. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. *Sleep*. 2003; 26(7):893-901.
30. Tozawa T, Mishima K, Satoh K, et al. Melatonin replacement therapy for rest-activity rhythm disorders in patients with senile dementia of the Alzheimer type. *Neurobiol Aging*. 1998;19(4S):S182.
31. Middleton B, Stone BM, Arendt J. Human circadian phase in 12:12 h, 200: <8 lux and 1000: <8 lux light-dark cycles, without scheduled sleep or activity. *Neurosci Lett*. 2002;329(1):41-44.
32. Van Someren EJW, Kessler A, Mirmiran M, Swaab DF. Indirect bright light improves circadian rest-activity rhythm disturbances in demented patients. *Biol Psychiatry*. 1997;41(9):955-963.
33. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
34. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. *Biol Psychiatry*. 1988;23(3):271-284.
35. Harwood DG, Ownby RL, Barker WW, Duara R. The factor structure of the Cornell Scale for Depression in Dementia among probable Alzheimer's disease patients. *Am J Geriatr Psychiatry*. 1998;6 (3):212-220.
36. Lawton MP. The Philadelphia Geriatric Center Morale Scale: a revision. *J Gerontol*. 1975;30(1): 85-89.
37. Ryden MB, Knopman D. Assess not assume–measuring the morale of cognitively impaired elderly. *J Gerontol Nurs*. 1989;15(11):27-32.
38. Lawton MP, Van Haitsma K, Klapper J. Observed affect in nursing home residents with Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci*. 1996; 51(1):P3-P14.
39. Helmes E, Csapo KG, Short JA. Standardization and validation of the Multidimensional Observation Scale for Elderly Subjects (MOSES). *J Gerontol*. 1987; 42(4):395-405.
40. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12(2):233-239.
41. de Jonghe JF, Kat MG, Kalisvaart CJ, Boelaarts L. Neuropsychiatric Inventory Questionnaire (NPI-Q): a validity study of the Dutch form [in Dutch]. *Tijdschr Gerontol Geriatr*. 2003;34(2):74-77.
42. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *J Gerontol*. 1989;44(3):M77-M84.
43. de Jonghe JF, Kat MG. Factor structure and validity of the Dutch version of the Cohen-Mansfield Agitation Inventory (CMAI-D). *J Am Geriatr Soc*. 1996; 44(7):888-889.
44. Holmes D, Teresi J, Weiner A, Monaco C, Ronch J, Vickers R. Impacts associated with special care units in long-term care facilities. *Gerontologist*. 1990; 30(2):178-183.
45. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. The index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. 1963; 185:914-919.
46. Ancoli-Israel S, Clopton P, Klauber MR, Fell R, Mason W. Use of wrist activity for monitoring sleep/wake in demented nursing-home patients. *Sleep*. 1997; 20(1):24-27.
47. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Med*. 2001;2(5):389-396.
48. Van Someren EJW. Improving actigraphic sleep estimates: how many nights? *J Sleep Res*. 2007; 16(3):269-275.
49. Van Someren EJW, Swaab DF, Colenda CC, Cohen W, McCall WV, Rosenquist PB. Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. *Chronobiol Int*. 1999;16(4): 505-518.
50. Gimeno V, Sagales T, Miguel L, Ballarin M. The statistical distribution of wrist movements during sleep. *Neuropsychobiology*. 1998;38(2):108-112.
51. Twisk JWR. *Applied Longitudinal Data Analysis for Epidemiology.* Cambridge, England: Cambridge University Press; 2003:280.
52. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data: application to the NIMH treatment of Depression Collaborative Research Program dataset. *Arch Gen Psychiatry*. 1993;50(9):739-750.
53. Petkova E, Teresi J. Some statistical issues in the analyses of data from longitudinal studies of elderly chronic care populations. *Psychosom Med*. 2002; 64(3):531-547.
54. Siddiqui O, Ali MW. A comparison of the random-effects pattern mixture model with last-observation-carried-forward (LOCF) analysis in longitudinal clinical trials with dropouts. *J Biopharm Stat*. 1998; 8(4):545-563.
55. Zhdanova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU. Melatonin treatment for age-related insomnia. *J Clin Endocrinol Metab*. 2001; 86(10):4727-4730.
56. Carman JS, Post RM, Buswell R, Goodwin FK. Negative effects of melatonin on depression. *Am J Psychiatry*. 1976;133(10):1181-1186.
57. Edinger JD, Bonnet MH, Bootzin RR, et al. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. *Sleep*. 2004;27(8):1567-1596.
58. Serfaty M, Kennell-Webb S, Warner J, Blizard R, Raven P. Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia. *Int J Geriatr Psychiatry*. 2002;17(12): 1120-1127.
59. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631): 386-389.
60. Van Someren EJW, Riemersma-Van Der Lek RF. Live to the rhythm, slave to the rhythm. *Sleep Med Rev*. 2007;11(6):465-484.
61. Burback D, Molnar FJ, St John P, Man-Son-Hing M. Key methodological features of randomized controlled trials of Alzheimer's disease therapy: Minimal clinically important difference, sample size and trial duration. *Dement Geriatr Cogn Disord*. 1999;10 (6):534-540.
62. Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. *Lancet Neurol*. 2007;6(9):782-792.