Melatonin effects on sleep, mood, and cognition in elderly with mild cognitive impairment

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Abstract: The effects of immediate-release melatonin on circadian rest-activity profiles, cognition, and mood were investigated in ten elderly individuals with self-reported sleep-wake disturbances. Melatonin (6 mg), administered 2 hr before habitual bedtime, enhanced the rest-activity rhythm and improved sleep quality as observed in a reduction in sleep onset latency and in the number of transitions from sleep to wakefulness. However, total sleep time was not significantly increased nor was wake within sleep significantly reduced. The ability to remember previously learned items improved along with a significant reduction in depressed moods. No side effects or contraindications were reported by any of our participants during the 10 day trials. These data suggest that melatonin can safely improve some aspects of sleep, memory, and mood in the elderly in short-term use.

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Introduction

Sleep-wake patterns, rest-activity cycles, body temperature, and hormonal secretions all display rhythms of approximately 24 hr [Moore-Ede et al., 1983]. Malfunctions of the circadian timekeeping mechanism may result in an inability of the organism to adapt to different environmental conditions. When the circadian generator, the suprachiasmatic nucleus (SCN), is ablated, a consequential loss of rhythmicity in several circadian functions is observed [Stephen and Zucker, 1972; Rusak and Zucker, 1979].

A disorganization of circadian rhythms is noted in the elderly, indicated by a dampened amplitude of the rest-activity cycle, body temperature, and hormonal rhythms [Bliwise, 1993; van Someren et al., 1993]. Circadian alterations have also been associated with changes in cognitive functioning [Prinz et al., 1982; Flicker et al., 1993]. A deficit in the amplitude of melatonin might underlie the disturbance of the sleep-wake cycle observed in the elderly, especially those who have dementia [Vitiello and Prinz, 1989; Witting et al., 1990; van Coeverden et al., 1991]. Possibly, the melatonin deficit is related to a selective deterioration of SCN

cell groups [i.e., arginine-vasopressin cells] [Swaab et al., 1985, 1996].

Another circadian disturbance in the elderly is a phase-advance in hormonal secretions and reduced amplitude (e.g., melatonin, prolactin, thyroid stimulating hormone, and cortisol) [van Coeverden et al., 1991]. Also, an increased intradaily variability and decreased interdaily stability of the circadian rhythm of activity has been described [McGinty and Stern, 1988; van Someren et al., 1996].

Several preliminary reports have suggested that melatonin can be used to treat advanced and delayed sleep phase syndromes [Zaidan et al., 1994; Deacon et al., 1995; Lewy et al., 1995] and sleep-wake maladaptation caused by shift work [Arendt et al., 1995]. Improvement has been observed in individuals with seasonal affective disorders [Lewy et al., 1987], sleep-wake disturbances induced by jet lag [Boulos and Rusak, 1982; Arendt et al., 1995], and insomnia [Garfinkel et al., 1995; Haimov et al., 1995].

Press accounts suggest that an increasing number of elderly individuals are currently ingesting melatonin to improve their sleep without careful monitoring to ascertain its safety and efficacy. Although reports have described improved sleep in

insomniacs, previous studies have not systematically examined melatonin effects on mood and cognition in the elderly. Further, by using different melatonin preparations, two recent melatonin studies have not found a significant increase in sleep duration [Garfinkel et al., 1995; Haimov et al., 1995]. Additionally, more recent preliminary data point to an increase in nocturnal activity level when patients with Alzheimer's disease were given a low dose of melatonin [Singer et al., 1997]. The present study sought to objectively investigate the effects of immediate-release melatonin on mood, cognition, rest-activity, and sleep in elderly individuals residing at home.

Methods

Participants

Ten community-residing elderly patients were recruited for this study by using the research registry at the Aging and Dementia Research Centers from New York University (NYU) Medical Center. Volunteers underwent the diagnostic workup at NYU, which included medical history, radiological examination, psychiatric assessment, neurological evaluation, and neuropsychological testing.

Irrespective of their level of cognitive impairment (see Results), patients were selected for this study on the basis of self-reported sleep-wake disturbances. Patients reported difficulty initiating sleep and frequent nocturnal awakenings. They were excluded if the following factors were present:

- Self-reported apnea syndrome and/or periodic limb movement
- Current or past history of significant medical illness.
- Disturbance in consciousness or symptoms of dementia other than Alzheimer's type dementia
- Neurodegenerative diseases other than Alzheimer's
- Metabolic or toxic disorders and severe sensory loss affecting cognitive assessment
- History of alcoholism and/or substance abuse
- Major psychiatric illness
- Evidence of infarction based on MRI scans

Procedure

Participants and caregivers were told that the purpose of the study was to investigate the therapeutic effect of melatonin on the circadian sleep-wake rhythm, cognitive, and noncognitive abilities in elderly individuals. The experimental protocol was described to participants and caregivers, including techniques of sleep-wake monitoring with the use

of wrist actigraph, neuropsychological assessment, and the sleepiness and the mood scales. Participants were asked to keep their daily routines and light-dark cycle as constant as possible for the duration of the study. They were asked to refrain from administration of antidepressant, hypnotic, or neuroleptic medications during the course of the study. Additionally, they were required to abstain from heavy consumption of alcohol and caffeinated beverages during data acquisition. Some participants were allowed to use certain medications only when it was advised by their physician.

Informed consent was obtained from all participants or from a spouse. An informed consent was also obtained from the caregivers. Participants were assured that their participation will be kept strictly confidential and acquired data will be used for research purposes only. They were advised to phone the laboratory if they wanted to know of the outcome of their participation in the study. The Ethics Committee at New York University Center, City College of New York, and the College of Staten Island approved the study. Melatonin as used in this study was manufactured by Cardiovascular Research, Ltd. Analysis conducted by ABCO Laboratories showed a level of purity of 99.62% when assayed.

This study was a double-blind, placebo-controlled, crossover investigation consisting of five phases.

Phase I. Qualified participants were recruited for the study and were mailed an invitation letter and a prospectus describing the purpose of the study. A week later, prospective participants were phoned to determine if they desired more information about the study. Those who were interested in participating were enrolled and were sent a 5 day sleep log, the sleepiness scale, and the mood scale to gather baseline data on their sleep-wake habits, daytime sleepiness, and mood. When the forms were returned, participants were scheduled for a semi-structured interview assessing sleep-wake patterns. Both patients and caregivers were interviewed to ascertain sleep pathology (e.g., episodes of sleep apnea and/or periodic limb movement). The study protocol was fully explained to both patients and caregivers and thereafter consent forms were obtained.

Phase II. During phase II of the study, participants were administered melatonin (6 mg) or an identical placebo for 10 days, 2 hr before bedtime based on their sleep log. This dosage was chosen on the basis of pharmacokinetic studies, which showed that melatonin has an estimated half-life of 30 to 60 min and remains in circulation for up to 4 hr [Aldhous et al., 1985]. It was postulated that this dosage would reduce sleep onset time and facilitate sleep consolidation. Further, subjective reports on mood,

sleepiness, and sleep were collected for 10 days. Actigraphic data were collected for the last 5 days of that phase. On the eleventh day, the patient received a visit by an investigator who conducted a neuropsychological evaluation including the following tests:

1. Alzheimer's Disease Assessment Scale [Mohs et al., 1984],
2. Digit Span [Forward and Backward] [Wechsler, 1981],
3. Digit Symbol Substitution [Wechsler, 1981],
4. Finger Tapping [Hiscock et al., 1987],
5. Mini Mental Status [Folstein et al., 1975].

After the neuropsychological tests were conducted, the investigator collected all forms that had been completed along with the actigraph.

Phase III. Phase III consisted of a washout period that lasted 5 days. Participants were not asked to wear the actigraph nor were they administered any treatment. However, sleepiness, mood, and sleep-wake logs were collected.

Phase IV. Procedures for sleep-wake diary and actigraphic monitoring for all participants were similar to phase II. Participants who received melatonin first were administered placebo and vice versa.

Phase V. Phase V served as a follow-up. Sleep-wake diary, sleepiness scale, and the visual analog scale were kept throughout that 5 day phase and collected by an investigator on the last day. Participants were debriefed after the completion of the study.

All participants were asked to wear an actigraph for sleep-wake monitoring. They were examined with a neuropsychological battery. Daily sleep-wake activity of these patients was recorded in a log. The Stanford Sleepiness Scale [Hoddes et al., 1973] and the Visual Analog Scale [Monk et al., 1989] were also completed. Information about patients whose level of cognitive impairment was more advanced was provided by their caregivers. An investigator called the patient/caregiver every day to inquire on activities for that day and the night before.

Instrumentation

For objective recording of the rest-activity patterns, wrist actigraphy was used to minimize intrusion into the life of the volunteers [Sadeh et al., 1995]. All actigraphic data were analyzed with the Actigraph Data Analysis Software (ADAS), which has been used in several studies to estimate sleep and wakefulness [Jean-Louis et al., 1996, 1997a,b]. In these studies, we have shown that the actigraph can be used reliably in normal as well as individuals with insomnia. Research findings from another group

have also demonstrated that actigraphy is a useful tool for discriminating sleep from wakefulness in patients with dementia [Ancoli-Israel et al., 1997].

Statistical analysis

Actigraphic data collected in phase II and IV were analyzed in three steps. Data were first visually inspected to ascertain actual time in bed. Time in bed was synchronized or adjusted by a trained scorer in cases where there was a discrepancy between reported bedtime and observed actigraphic counts; discrepancies were mostly noted for the reported time at which participants went to bed.

Second, the data were analyzed to yield a number of nocturnal sleep-wake parameters. Variables derived from the actigraphic data including total sleep time (TST), sleep efficiency index (SEI), wake after sleep onset (WASO), total wake time (TWT), and transition from sleep to wakefulness were averaged over the 5 day period to allow meaningful comparisons in repeated-measures MANOVA.

Third, ADAS was used to determine possible changes in circadian amplitude in rest-activity patterns, calculated over a lag of 1,700 minutes with an autocorrelation function; these lags were used to capture activity rhythm that may be more than 24 hr (1,440 min). Additionally, to ascertain possible phase shifts in the rest-activity pattern, these data series were further analyzed with cosine-fitting procedures as described in ACTION3 (Ambulatory Monitoring, Inc., Ardsley, NY).

Cognitive abilities and mood profiles were compared across the two treatment conditions with a repeated-measures MANOVA procedure. These measures were derived from the neuropsychological evaluations, which included immediate and delayed memory, digit span, digit symbol, attention, concentration, finger tapping, and depressed moods.

Results

Six women and four men (mean age: 68.8 ± 15.8) participated in the study. Nine volunteers were initially assigned a diagnostic classification based on the observed level of severity according to the dementia rating system known as the global deterioration scale (GDS). According to this scale, scores range from 1, indicating no clinically manifest cognitive impairment to 7, when patients show severe cognitive impairment [Reisberg et al., 1988]. Two volunteers received a diagnosis of Alzheimer's disease (GDS = 4 and 5) and met the diagnostic standards as established by the National Institute of Neurological and Communicative Disorders and Stroke, the Alzheimer's Disease and Related Dis-

orders Association and the DSM-IV criteria. Five volunteers had a GDS score of 3 and two participants had a score of 2. One participant did not undergo the diagnostic workup from NYU. He was referred to the study coordinator from another source and was included in the study because his cognitive profile was within the range of the other nine volunteers (e.g., Alzheimer's Disease Assessment scale = 7, Mini Mental Status = 29, compared to a median score of 11and 28, respectively, for the remaining sample).

Effects of melatonin on actigraphic variables

Repeated-measures MANOVA indicated a significant treatment effect on some of the variables entered in the procedure (see Table 1). These variables were the circadian amplitude of rest-activity cycle, sleep onset latency, and transition from sleep to wakefulness [$F(1, 9) = 5.16$, $P = .049$; $F(1, 9) = 8.20$, $P = 018$; $F(1, 9) = 10.08$, $P = .011$, respectively]. However, the present analyses showed no significant effects of melatonin on TST, TWT, and WASO (see Table 2 for mean values). An important trend toward improvement in sleep efficiency index was noted under the melatonin condition [$F(1, 9) = 3.40$, $P = .098$]. Additionally, the cosine-fitting analyses showed a phase shift of the rest-activity pattern of one hour (placebo = 14:22, melatonin = 15:22), which did not, however, reach significance.

Effects of melatonin on neuropsychologic variables

Melatonin had significant effects on some of the neuropsychologic variables entered into the model (see Table 3). Repeated-measures MANOVA indicated that melatonin significantly reduced depressed moods and enhanced the ability to recall previously

Table 1. MANOVA for rest-activity and sleep data[a]

Omnibus repeated-measures F-test for actigraphic variables

Test	Value	F	P
Hotelling's	2.003	4.674	.043

Univariate F-test for actigraphic data

Variable	Melatonin	Placebo	F	P
Amplitude	.54 (.21)	.41 (.24)	5.16	.045
Sleep onset latency	14.70 (7.21)	26.08 (10.97)	8.20	.018
Transition	17.75 (7.79)	31.20 (11.37)	10.08	.011

[a]Among the variables entered, rest-activity amplitude was significantly higher, whereas sleep onset latency and transition between sleep and wakefulness were significantly lower under melatonin administration. Total sleep time, total wake time, sleep efficiency index, and wake after sleep onset were not statistically significant. Values under melatonin and placebo represent means and standard deviations.

Table 2. Sleep/wake activity parameters derived from the actigraph with ADAS[a]

	Melatonin effects on sleep in the elderly			
	Melatonin		Placebo	
Variable	Mean	SD	Mean	SD
Transition	17.75*	7.79	31.20	11.37
Wake after sleep onset	20.78	7.78	26.78	6.28
Total wake time	35.47	9.89	52.49	13.22
Sleep efficiency index	.93	.03	.90	.02
Total sleep time	458.47	51.91	493.25	68.36
Sleep onset latency	14.70*	7.21	26.08	10.97

[a]Transition from sleep to wakefulness and sleep onset latency showed significant reduciton associated with melatonin administration (*indicates $P < 0.05$). Sleep efficiency index showed a trend toward improvement ($P = .09$).

learned items from the Alzheimer's Disease Assessment Scale [$F(1, 7) = 7.36$, $P = .024$; $F(1, 9) = 9.75$, $P = .021$, respectively]. Interestingly, the ability to concentrate marginally improved with melatonin [$F(1, 9) = 3.46$, $P = .096$]. No significant effects were observed on the ability to perform these tasks: immediate recall and recognition, digit span, digit symbol, and finger tapping. However, there was no detrimental effect on cognition associated with melatonin.

Discussion

To ascertain the safety and efficacy of melatonin in addressing sleep-wake disturbances associated with circadian abnormalities, this study investigated several effects of melatonin in the elderly. Parameters examined included aspects of sleep-wake patterns, circadian rest-activity profiles, cognition, and mood.

Table 3. MANOVA assessing treatment effects on neuropsychologic variables[a]

Omnibus repeated-measures F-test for neuropsychologic variables

Test	Value	F	P
Hotelling's	15.946	11.960	.035

Univariate F-test for neuropsychologic data

Variable	Melatonin	Placebo	F	P
Delayed recall	5.14 (2.73)	3.10 (2.47)	9.75	.021
Depressed moods	.60 (.70)	1.20 (.92)	7.36	.024

[a]Among the variables entered, delayed recall and depressed moods showed significant effects of melatonin. Patients expressed less depressed moods and more items were recalled on the delayed recall task under the melatonin condition. Immediate recall, digit span, digit symbol substitution, and finger tapping did not show any significant changes. Scores for delayed recall ranged from 0 to 10, and with a score of 0 indicating a poor ability to remember. Depressed mood was rated on a scale of 0 to 5 from the Alzheimer's Disease Assessment Scale. A value of 0 represented the absence of depressed moods.

Although the present analyses were based on individuals with no laboratory diagnosed sleep disorders, significant changes in the rest-activity patterns were observed when melatonin was administered. Notably, the circadian rest-activity amplitude was enhanced, reaching comparable level with elderly volunteers with no major sleep complaints [Jean-Louis et al., 1997c]. Melatonin significantly improved sleep quality in these elderly individuals by reducing their sleep onset latency and the number of transitions from sleep to wakefulness. The improvement observed in these sleep parameters is consistent with previous reports of sleep-inducing effects of melatonin in insomniacs [Garfinkel et al., 1995; Haimov et al., 1995].

The present data reveal a strong trend towards improvement in sleep quality as determined by SEI. The lack of statistical significance for SEI may be explained by the high reference level of SEI for this sample (average SEI = 90%). Although participants in this sample were characterized by a relatively low level of rest-activity amplitude, they may not have a sleep problem identifiable by wrist activity monitoring. The complaint of sleep/wake disturbance reported in the initial interview may have reflected misperception of sleep, as has been found by other investigators [Hauri and Wisbey, 1992; Foley et al., 1995].

It is important to note that melatonin did not significantly increase the amount of sleep that volunteers accumulated in the present study or in previous ones [Garfinkel et al., 1995; Haimov et al., 1995]. In addition, inconsistent results have been found regarding wake within sleep. Treatment regimens for individuals with insomnia are traditionally intended to increase in-bed sleep time, which should translate into better perception of sleep and enhanced daytime functioning. These results did not indicate that melatonin can substitute for behavioral treatment or hypnotics. In fact, although not statistically significant, we observed an average reduction of 35 min associated with melatonin administration. This reduction in sleep duration did not, however, affect their sleep efficiency as a marginal improvement was noted.

Perhaps, the effects of immediate-release melatonin can mostly be observed in its ability to stabilize the rest-activity cycle (i.e., to reestablish a proper circadian distribution of rest-activity). The significant increase in circadian amplitude and the 1 hr shift in rest-activity found in the present study supports that notion and indicates that immediate-release melatonin treatment might potentially engender better sleep with long-term use. The phase delay under the melatonin condition was observed across patients and does not seem to reflect residual effect of melatonin.

Pharmacokinetic studies have shown that immediate-release melatonin has an estimated half-life of 30 to 60 min and may only be found in circulation for up to 4 hr after administration of immediate-release preparations [Aldhous et al., 1985]. As suggested by other investigators, it is conceivable that possible benefits of melatonin in the elderly can be gained with optimally scheduled circadian administration since, seemingly, its effects are mediated through a chronobiologic mechanism. These data suggest that elderly patients who desire to increase their sleep time may not benefit from melatonin. Investigations with a larger sample and longer regimens might provide a more conclusive statement regarding sleep potentiation with melatonin.

The present study showed significant benefits of melatonin on mood and on performance with no deleterious effects. A number of trends toward positive effects on both cognitive and noncognitive parameters were noted; which may prove important in larger samples. Further, although these elderly volunteers showed some cognitive impairment based on the global deterioration scale, baseline intellectual functioning of most participants was within the range of cognitive ability exhibited by normal elderly persons based on mini mental status scores.

Melatonin showed a positive effect on delayed recall, which warrants further probing into a possible role of melatonin regarding its effect on memory. This effect may be very specific since there was no significant variation in immediate recall and/or recognition. An increase in these measures might have suggested a change in performance due to improved sleep under melatonin. Melatonin may be acting on the mechanism responsible for memory consolidation as seen in an enhanced capacity to recall only previously learned items.

The observation of a significant reduction in depressed moods was particularly interesting in view of the suggested role of melatonin as a synchronizing neurohormone with possible affective correlates. This finding supports the report of a decrease in sadness noted subsequent to acute melatonin ingestion in a young normal sample we have previously studied [Jean-Louis et al., 1997d].

These data are important and suggest that a longer treatment regimen might yield better results regarding cognitive and noncognitive behavior. Better results could also be obtained in an elderly sample characterized by greater cognitive impairment. Future investigations should address the mechanism of action of melatonin on cognitive processes particularly in demented individuals. Finally, these results indicate that there are no detrimental effects associated with chronic administration of a pharmacological dose of melatonin as used in this

study. Additionally, no side effects or contraindications were reported by any of our participants during the ten-day trials.

Literature cited

ALDHOUS, M., C. FRANEY, J. WRIGHT, J. ARENDT (1985) Plasma concentrations of melatonin in man following oral absorption of different preparations. Br. J. Clin. Pharmacol. 19: 517–521.

ANCOLI-ISRAEL, S., P. CLOPTON, M.R. KLAUBER, R. FELL, W. MASON (1997) Use of wrist activity for monitoring sleep/wake in demented nursing-home patients. Sleep 20:24–27.

ARENDT, J., S. DEACON, J. ENGLISH, S. HAMPTON, L. MORGAN (1995) Melatonin and adjustment to phase shift. J. Sleep Res. 2:74–79.

BLIWISE, D.L. (1993) Sleep in normal aging and dementia. Sleep 16:40–81.

BOULOS, Z., B. RUSAK (1982) Phase-response curves and the dual oscillator model of circadian pacemakers. In: Vertebrate Circadian Systems. D.S. Aschoff, and G. Groos, eds. Springer, Berlin. pp. 215–223.

DEACON, S., J. ARENDT (1995) Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. Brain Res. 688:77–85.

FLICKER, C., S.H. FERRIS, B. REISBERG (1993) A two-year longitudinal study of cognitive function in normal aging and Alzheimer's disease. J. Geriatr. Psychiatry Neurol. 6:84–96.

FOLEY, D., A. MONJAN, S.E.AL. BROWN (1995) Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep 18:425–432.

FOLSTEIN, M.F., S.E. FOLSTEIN, P.R. McHUGH (1975) "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J. Psychiatric Res. 12:189–198.

GARFINKEL, D., M. LAUDON, D. NOF, N. ZISAPEL (1995) Improvement of sleep quality in elderly people by controlled-release melatonin. Lancet 346:541–544.

HAIMOV, I., P. LAVIE, M. LAUDON, P. HERER, C. VIGDER, N. ZISAPEL (1995) Melatonin replacement therapy of elderly insomniacs. Sleep 18:598–603.

HAURI, P.J., J. WISBEY (1992) Wrist actigraphy in insomnia. Sleep 15:293–301.

HISCOCK, M., M. KINSBOURE, M. SAMUELS, A. KRAUSSE (1987) Dual task performance in children: Generalized and laterized effects of memory encoding upon the rate and variability of cocurrent finger tapping. Brain Cogn. 6:24–40.

HODDES, E., V. ZARCONE, H. SMYTHE, R. PHILLIPS, W. DEMENT (1973) Quantification of sleepiness: A new approach. Psychophysiology 10:431–436.

JEAN-LOUIS, G., H. VON GIZYCKI, F. ZIZI, J. FOOKSON, A. SPIELMAN, J. NUNES, R. FULLILOVE, H. TAUB (1996) Determination of sleep and wakefulness with the actigraph data analysis software (ADAS). Sleep 19:739–743.

JEAN-LOUIS, G., H. VON GIZYCKI, F. ZIZI, A.J. SPIELMAN, P. HAURI, H. TAUB (1997a) The actigraph data analysis software (ADAS). I. A novel approach to scoring and interpreting sleep/wake Perceptual Motor Skills 85:207–216.

JEAN-LOUIS, G., H. VON GIZYCKI, F. ZIZI, A.J. SPIELMAN, P. HAURI, H. TAUB (1997b) The actigraph data analysis software (ADAS). II. A novel approach to scoring and interpreting sleep/wake Perceptual Motor Skills 85:219–226.

JEAN-LOUIS, G., F. ZIZI, H. VON GIZYCKI, J. GAGLIO, A.J. SPIELMAN, J. FOOKSON, R. MANBER, H. TAUB (1997c) Circadian rest-activity rhythm in different age group as determined by actigraphy. Sleep Res. 26:668.

JEAN-LOUIS, G., F. ZIZI, H. VON GIZYCKI, J. DIPALMA, J. NUNES, A.J. SPIELMAN, C. STAMPI, H. TAUB (1997d) Acute effects of melatonin therapy on behavior, mood, and cognition. Sleep Res. 26:108.

LEWY, A.J., R.L. SACK, L.S. MILLER, T.M. HOBAN (1987) Antidepressant and circadian phase-shifting effects of light. Science 235:352–354.

LEWY, A.J., R.L. SACK, M.L. BLOOD, V.K. BAUER, N.L. CUTLER, K.H. THOMAS (1995) Melatonin marks circadian phase position and resets the endogenous circadian pacemaker in humans. Ciba Found. Symp. 183:303–317.

McGINTY, D., N. STERN (1988) Circadian and sleep-related modulation of hormone levels: changes with aging. In: Endocrinology of Aging. J.R. Sowersand and J.V. Felicetta, eds. Raven, New York, pp. 163–172.

MOHS, R., W. ROSEN, K. DAVIS (1984) The Alzheimer's disease assessment scale: An instrument for assessment of treatment efficacy. Psychophysiology 19:448–50.

MONK, T.H., M.L. MOLINE, J.E. FOOKSON, S.M. PEETZ (1989) Circadian determinants of subjective alertness. J. Biol. Rhythms 4:393–404.

MOORE-EDE, M.C., C.A. CZEISLER, G.S. RICHARDSON (1983) Circadian timekeeping in health and disease. Part 1. Basic properties of circadian pacemakers. N. Engl. J. Med. 309:469–476.

PRINZ, P.N., E.R. PESKIND, P.P. VITALIANO, M.A. RASKIND, C. EISDORFER, N. ZEMCUZNIKOV, C.J. GERBER (1982) Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. J. Am. Geriatr. Soc. 30:86–93.

REISBERG, B., S.H. FERRIS, M.J. DE LEON, T. CROOK (1988) Global deterioration scale (GDS). Psychopharmacol. Bul. 24:661–663.

RUSAK, B., I. ZUCKER (1979) Neural regulation of circadian rhythms. Physiol. Behav. 59:449–526.

SADEH, A., P.J. HAURI, D.F. KRIPKE, P. LAVIE (1995) The role of actigraphy in the evaluation of sleep disorders. Sleep 18:288–302.

SINGER, C.M., M.T., MOFFIT, E.D. COLLING, R.J. HUGHES, N.L. CUTLER, R.L. SACK, A.J. LEWY (1997) Low dose melatonin administration and nocturnal activity levels in patients with Alzheimer's disease. Sleep Res. 26, 752.

STEPHAN, F., M. BERBERLY, R. MOSS (1972) Efferent connections of the rat suprachiasmatic nucleus. Neuroscience 6:2625–2642.

SWAAB, D.F., E. FLIERS, T.S. PARTIMAN (1985) The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain Res. 342:37–44.

SWAAB, D.F., E.J. VAN SOMEREN, J.N. ZHOU, M.A. HOFMAN (1996) Biological rhythms in the human life cycle and their relationship to functional changes in the suprachiasmatic nucleus. Prog. Brain Res. 111:349–368.

VAN COEVORDEN, A., J. MOCKEL, E. LAURENT, M. KERKHOFS, M. L'HERMITE-BALERIAUX, C. DECOSTER, P. NAVE, E. VAN CAUTER (1991) Neuroendocrine rhythms and sleep in aging men. Am. J. Physiol. 260:E651–E661.

VAN SOMEREN, E.J., E.E. HAGEBEUK, C. LIJZENGA, P. SCHELTENS,

S.E. De Rooij, C. Jonker, A.M. Pot, M. Mirmiran, D.F. Swaab (1996) Circadian rest-activity rhythm disturbances in Alzheimer's disease. Biol. Psychiatry 40:259–70.

Van Someren, E.J., M. Mirmiran, D.F. Swaab (1993) Non-pharmacological treatment of sleep and wake disturbances in aging and Alzheimer's disease: Chronobiological perspectives. Behav. Brain Res. 57:235–253.

Vitiello, M.V., P.N. Prinz (1989) Alzheimer's disease: Sleep and sleep/wake patterns. Clin. Geriatr. Med. 5:289–299.

Wechsler, D. Wais-R M. (1981) Adult Intelligence Scale-Revised. San Antonio, The Psychological Corporation.

Witting, W., I.H. Kwa, P. Eikelenboom, M. Mirmiran, D.F. Swaab (1990) Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. Biol. Psychiatry 27:563–572.

Zaidan, R., M. Geoffriau, J. Brun, J. Taillard, C. Bureau, G. Chazot, B. Claustrat (1994) Melatonin is able to influence its secretion in humans: Description of a phase-response curve. Neuroendocrinology 60:105–112.