

## Melatonin for treatment of sundowning in elderly persons with dementia – a preliminary study

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### Abstract

This pilot study investigated the impact of melatonin administration as a clinical intervention for improving sleep and alleviating sundowning in 11 elderly nursing home residents who suffer from dementia. Melatonin is a hormone produced and secreted by the pineal gland in response to darkness, which plays a major role in the induction and regulation of sleep. Melatonin production decreases with age. Age-related sleep disorders are frequently associated with disruption of circadian cycle rhythms, and sometimes with 'sundowning'. Sundowning refers to the manifestation of agitation and/or confusion in the evening hours. Agitation has been linked to sleep disorders. Analysis revealed a significant decrease in agitated behaviors in all three shifts, and a significant decrease in daytime sleepiness. There was a nonsignificant decrease in latency (time to fall asleep) during the evening shift and no significant changes were reported in night-time sleep ratings. The results of this study are important, because finding ways of decreasing sundowning in elderly persons may improve their well being, alleviate the burden of the caregivers, and even enable caregiving in a less restrictive environment. © 2000 Published by Elsevier Science Ireland Ltd.

*Keywords:* Melatonin; Agitation; Sundowning; Behavior problems in dementia

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## **1. Introduction**

The present study was undertaken in order to evaluate the possible therapeutic effect of exogenous melatonin on sundowning, the agitated behavior manifested during the evening hours, in a population of demented, elderly nursing home residents.

Agitation refers to inappropriate verbal, vocal or motor behavior, which is not explained by apparent needs or by confusion per se (Cohen-Mansfield and Billig, 1986). Agitation is not a diagnostic term but is rather used by clinicians for a group of symptoms which may reflect an underlying disorder. Whereas the term ‘disruptive behaviors’ refers to agitated behaviors, we prefer ‘agitation’ because this term is more commonly used by professionals involved in long-term care for elderly individuals. Agitation represents a major problem for elderly persons and for their caregivers (Teri et al., 1988; Hamel et al., 1990). It affects the quality of life of elderly persons in the community, their likelihood of entering a long-term care facility and their specific needs in such a facility. Some of the practices currently employed to deal with agitation in nursing homes residents include psychotropic medication, physical restraints, a high ratio of staff to residents and special environmental designs.

Although agitated behaviors are frequently considered as one entity by caregivers, our previous research indicated that these behaviors differ in their clinical manifestations and significance. At least three main subgroups of behaviors can be defined separately: verbally agitated behaviors such as constant repetitive talk or complaining; physically nonaggressive behaviors such as aimless wandering or inappropriate disrobing; and aggressive behaviors such as hitting or kicking (Cohen-Mansfield et al., 1989a). All types of agitation are related to cognitive impairment, though they peak at different levels of cognitive decline (Cohen-Mansfield et al., 1995a).

The relationship between agitation and sleep needs to be examined within the context of the well-documented age-related changes in sleep patterns in the elderly (Miles and Dement, 1980; Spiegel, 1981; Zepelin, 1983; Bliwise, 1993). Sleep disturbances in the elderly have been linked to cognitive impairment (Loewenstein et al., 1982). Sleep disturbances in elderly persons with Alzheimer’s disease include fragmented sleep with frequent awakenings, reduced stage three (NREM) non rapid eye movement and (REM) rapid eye movement sleep, and no stage four NREM sleep (Prinz, 1982a; Prinz et al., 1982; Allen et al., 1983; Vitiello et al., 1990).

Several studies have shown a relationship between agitation and sleep in elderly persons (Cohen-Mansfield and Marx, 1990; Cohen-Mansfield et al., 1995b). In general, increased levels of agitation are observed along with an increased incidence of sleep disturbances (e.g., frequency of awakenings, late sleep onset times, early wake-up time). Furthermore, agitated behaviors may be exacerbated by fatigue (Cohen-Mansfield et al., 1995b).

The correlation between agitation and sleep disturbances may explain the related concept of sundowning. This concept indicates episodes of agitation which are more frequent and/or severe in the evening hours (Cohen-Mansfield et al., 1989b; Bliwise,

1993, 1994; McGaffigan and Bliwise, 1997). The sundowning syndrome is associated with increased burden on caregivers because it occurs during the hours in which caregivers are least available, when family caregivers are tired and ready to rest, and when institutional caregiving staff are at the lowest staffing levels. Therefore, if a phaseshift of this behavior is induced, it would alleviate the burden and cost the caregivers.

Sundowning is associated with increased daytime sleep and disrupted night sleep (Hess, 1997). This phenomenon may be related to dysfunction of circadian rhythmicity (Okawa et al., 1991), which may, in turn, be secondary to either spontaneous or induced awakening from sleep. Alternatively, circadian changes in both sleep and behavior may be related to a primary defect in translating the external light/dark to the internal sleep/wake cycles.

Melatonin (5-methoxy-*N*-acetyltryptamine) is a hormone secreted principally by the pineal gland in response to darkness under normal environmental conditions (Arendt, 1988; Geoffriau et al., 1998; Pierpaoli, 1998). Melatonin affects sleep onset in humans by its synchronizing effect on the internal biological clock (Arendt, 1988; Dawson & Encel, 1993; Gross & Gysin, 1996). Endogenous serum melatonin levels are usually lower in older people than in younger adults; however, serum melatonin levels induced by low oral doses of exogenous melatonin are higher and more variable in older adults as compared to young adults (Zhdanova et al., 1998).

Several studies have demonstrated that melatonin can improve sleep and affect the circadian rhythm in humans, though the results are not unanimous. Okawa et al. (1998) found that 1–3 mg of melatonin given before sleep, corrected circadian rhythm sleep disorders in over half (six out of 11) of the patients (eight males and three females aged 16–46). In a series of studies with young adults (Zhdanova et al., 1995, 1996, 1998), low oral doses of melatonin (0.3 or 1.0 mg) were found to decrease sleep onset latency and latency to stage two sleep. In a 16-day trial, Singer et al., (1995a) did not find any effect of 0.2 mg sustained release melatonin on healthy elderly persons with no sleep disorders; however, they did find modest improvement in sleep efficiency and wake after sleep onset (WASO) in eight healthy elderly persons without sleep disorders when using 50 mg dose of melatonin for 16 days (Singer et al., 1995b). Effects were more pronounced during the last days of trial than during the first days. Haimov et al. (1995) investigated the effect of melatonin administration in melatonin-deficient elderly insomniacs. They found that a 1 week treatment with 2 mg sustained-release melatonin was effective for sleep maintenance, while sleep initiation was improved by regular melatonin. Both sleep maintenance and initiation were improved by prolonged (2 months) administration of 1 mg sustained release melatonin. Garfinkel et al. (1995) found that administration of 2 mg controlled release melatonin tablets improved sleep quality in community-dwelling elderly persons who had decreased endogenous melatonin production and suffered from sleep problems. Similar beneficial effects were found in elderly insomniacs who had been chronically treated with benzodiazepine (Garfinkel et al., 1997). A review of the use of controlled-release melatonin for insomnia in elderly people is provided in Zisapel and Garfinkel (1998).

Disruption of the circadian rhythm in dementia (Sloan et al., 1996) and melatonin's efficacy in resetting the circadian clock, suggest that melatonin may have beneficial effects in patients with dementia who suffer from this dysrhythmicity and to their caregivers. Those experiencing sundowning would probably be the most likely to benefit from melatonin. One should remember, however, that the exact nature and etiology of sundowning are far from being clear. Even the significance of sundowning in contrast to morning-time agitation has been questioned (Cohen-Mansfield et al., 1989b). Two plausible alternative explanations are that (1) sundowning is agitation induced by fatigue in patients who have difficulty sleeping, or (2) sundowning involves evening time agitation caused by other reasons which occurs in the evening because the older person has been awake for several hours. If the patient was to sleep at night and spend more time awake during the day, this agitation might have been manifested during the day. The first model would suggest that if melatonin improves the quantity and quality of sleep during the evening and night hours, the person would be less tired, and overall agitation would decrease. According to the latter model, if evening and night-time sleep would improve because of melatonin administration, agitation during that time would decrease because the person would be asleep. However, agitation during the daytime would increase because of decreased sleep-time during the day, and more time available to manifest agitation.

This pilot study investigated the effect of melatonin as a clinical intervention for improving sleep and alleviating sundowning in institutionalized elderly persons who suffer from dementia. Our hypotheses were that with the administration of melatonin before night sleep time:

1. Sleep would occur more during night time and less during day time hours.
2. Agitated behaviors would decrease in frequency, at least during the evening and night shifts.
3. Agitated behaviors would shift more to daytime hours.

## **2. Methods**

### *2.1. Participants*

Participants were 11 nursing home residents of a large suburban nursing home. Eight of the participants were female. The mean age was 85, with a range of 79–92 years. Five of the participants were widowed, five were married, and one was single. All suffered from cognitive impairment according to the minimum data set (Hawes et al., 1995; Frederiksen et al., 1996): Four were rated as 'modified independence', five were rated as 'moderately impaired', and two were rated as 'severely impaired'.

### *2.2. Intervention*

Participants received a tablet containing melatonin every evening for three weeks as part of their medical treatment. The commercially available tablets of oral

melatonin were supplied to the residents by the nursing home pharmacy. Most residents received 3 mg of melatonin per evening; two residents received a reduced dose of melatonin, the first was started on 1 mg which was increased to 3 mg after 2 days, and the other received 3 mg melatonin only every other evening, alternating with 5 mg Zolpidem Tartrate. Residents received their dose of melatonin approximately 1 h prior to their planned bed time with the exception of one resident for whom the time was changed to 18:00 h on the 3rd week of melatonin administration.

### *2.3. Design and procedure*

The study design was an open label clinical trial undertaken to examine safety, and to obtain preliminary data on melatonin's effectiveness. The research staff members were notified by the physicians on their intent to prescribe melatonin to specific residents for the treatment of sleep disturbances and/or evening-time agitation.

In order to explore the impact of melatonin, nursing staff members on all three of the 8 h shifts (7:00–15:00, 15:00–23:00, 23:00–7:00 h) were asked to rate the sleep and agitation of each resident. Ratings were completed independently by a member of the nursing staff who was most closely involved with the resident at the end of each nursing shift. They were asked to rate the resident during a baseline week, then during the 3 weeks of melatonin administration.

### *2.4. Assessments*

#### *2.4.1. Agitation*

Agitation as assessed by the short form Cohen-Mansfield Agitation Inventory (CMAI). The inventory consists of 14 agitated behaviors, each rated on a five-point scale of frequency ('one' indicates that the resident never engages in the specific agitated behavior and 'five' that the resident manifests the behavior on the average of several times an hour) (Werner et al., 1994). Inter-rater reliability was assessed by two independent nursing staff members, who rated 19 residents. The inter-rater agreement rate was calculated two ways: It was 81.8% based on exact agreement, and 92.3% when based on a 0- or 1-point discrepancy (Werner et al., 1994). Based on previous findings (Cohen-Mansfield et al., 1995c), four syndromes were used: Physically aggressive behaviors (PAG) (such as hitting and kicking), physically nonaggressive behaviors (PNAB) (such as pacing, disrobing and handling things inappropriately), verbally agitated behaviors (VNAB) (such as repetitious vocalizations and complaining), and verbally aggressive behaviors (VAG) (such as cursing or screaming). For each syndrome of agitation, an index estimating the overall frequency of occurrence of the syndrome was calculated. The procedure for calculating the index involved the following stages: First, we determined the most frequently occurring behavior of those included in the syndrome; when two or more behaviors occurred at a low frequency, we specified that a behavior occurred at the next higher level. For example, if two physically aggressive behaviors occurred at a

frequency of ‘several times a week,’ this was equated to a score of a single behavior occurring ‘once or twice a day’. The highest score between any single behavior and the aggregate scores formed an index of the syndrome that was used in subsequent analyses.

#### 2.4.2. Sleep

Sleep ratings were adapted from the nurses’ ratings of sleep patterns questionnaire (NRSPQ), which utilizes independent raters (nursing staff). The nursing staff are required to routinely check on the residents every 2 h (Cohen-Mansfield and Marx, 1990). The instrument measures the following dimensions of sleep: Number of hours of sleep; latency-length of time to fall asleep; frequency of spontaneous awakenings; length of average wake period; hour of awakening in the morning; and external disruptions to sleep. In the adapted version, the following items were included:

*2.4.2.1. The night shift (23:00–7:00 h) sleep questionnaire tapped the following dimensions of sleep.* Latency-length of time to fall asleep (after retiring to bed). This item was rated on the following scale: 0, was asleep at the beginning of the shift; 1, fell asleep immediately; 2, fell asleep in less than 30 min; 3, fell asleep between 30 and 60 min; 4, fell asleep between 1 and 2 h; and 5, took more than 2 h to fall asleep; 6, did not sleep during shift.

Frequency of spontaneous awakenings. How often had the participant spontaneously woken up during the night. This was assessed using the following scale: 1, never; 2, once; 3, several times; 4, awake most of the night; 5, did not sleep during shift.

Length of average wake period. The participant’s average duration of wake periods (spontaneous awakenings only) during the night was rated using the following scale: 0, did not wake up; 1, less than 3 min; 2, from 3 to 15 min; 3, from 16 to 30 min; 4, from 31 to 60 min; 5, more than an hour; and 6, awake most of the night.

The number of hours of sleep. The number of hours the resident slept during each particular shift.

*2.4.2.2. The evening shift (15:00–23:00 h) sleep questionnaire tapped the following dimensions of sleep.* Latency-length of time to fall asleep (after retiring to bed); frequency of spontaneous awakenings; and length of average wake period. These were rated in the same way as the night-time shift.

*2.4.2.3. The daytime shift (7:00–15:00 h) sleep questionnaire tapped the following dimensions of sleep.* The hour at which each participant woke up in the morning.

Drowsiness of the participant. How frequently had the resident appeared ‘drowsy’ or sleepy during the day. This was rated on a six-point scale with one indicating never, and six all or nearly all of the time.

Frequency of naps. How frequently had the participant fallen asleep during the day. This was rated on a six-point scale with one indicating never and six all or nearly all of the time.

How long had the participant usually napped. The average duration of the participants' naps was rated on a five-point scale with one indicating less than 3 min and five indicating more than an hour.

### 3. Results

No adverse effects were noted and no difficulty in procedures of handling the melatonin were encountered. However, one resident was withdrawn from the study. Prior to entering the study, this patient was severely agitated. During baseline, he fractured his right shoulder. The staff tried to control his pain and agitation with different medications but to no avail. His behavior included removing the arm sling, bed alarm and night clothes. Therefore, only ten residents were available for the hypothesis testing. During the study, the other participants did not have any febrile or other acute diseases.

The testing of hypotheses is described below:

(i) With melatonin, sleep would occur more during night time and less during day time.

Analyses involved paired *t*-tests comparing sleep variables during week 1 (baseline) to week 4 (after 3 weeks on melatonin). Results are presented in Table 1. Generally, sleepiness during the daytime shift decreased significantly but no significant differences were found in evening and night-time sleep. There was a trend in the hypothesized direction for latency to decrease, but this change was not statistically significant.

(ii) Agitated behaviors would decrease in frequency.

The change in the frequency of agitation manifested by the residents was examined via paired *t*-tests comparing the levels of each syndrome of agitation during the baseline week to that of the 4th week, following 3 weeks of melatonin administration. The results are presented in Table 2. Reduction in the frequency of agitated behavior was found in most indices: Five decreases were significant at the 0.05 level, and nine at the 0.1 level, which was considered here because of the small number of participants. Most impressive are the reductions in agitated behaviors during the evening shift. Examining weekly changes for individual participants on the evening shift, the following was noted: For physically nonaggressive behaviors (PNAB), seven of the ten residents manifested such behaviors at baseline. Of these, five manifested consistent decline after melatonin administration and two did not show a consistent change. Out of the three who did not manifest any such behavior at baseline, two remained the same throughout the follow-up period, and one showed just a slight increase on week 4 from a rating of one to 1.2. The same five residents who showed decreased PNAB also showed a decrease in verbally agitated behaviors, as did another resident who did not change in his level of physically nonaggressive behaviors. Concerning the other residents, two did not manifest any verbally agitated behaviors during the trial and one showed some increase (this is not the same individual as the one manifesting slight increase in physically nonaggressive behaviors).

As for the aggressive behaviors, only four patients showed any physically aggressive behaviors at baseline and all exhibited a decrease in these manifestations following melatonin administration. The other six did not manifest any such behaviors before or throughout the trial. For verbally aggressive behaviors, the results were less distinctive, with two residents showing consistent decreases, two residents never manifesting the behaviors, and the other six fluctuating during the trial.

(iii) Agitated behaviors would shift more to daytime occurrence. This hypothesis was not confirmed. Daytime agitation did not increase. (Table 2.)

#### 4. Discussion

The present pilot study suggests that melatonin can be administered safely to this population of elderly residents with dementia. It also presents some promise for melatonin's utility in decreasing sundowning, the evening time agitation.

Table 1  
Sleep scores (unless otherwise noted  $n = 10$ )

<i>Day shift</i>				
Variable	Week 1 index	Week 4 index	<i>t</i> -test value	<i>P</i> -value (1-tailed)
How often resident appeared drowsy*	3.10	2.24	3.092	0.0075
How long resident napped*	2.67	2.00	2.317	0.0245
How often resident napped*	2.80	1.88	2.856	0.0105
Time resident awoke in the morning*	6.69	6.62	0.470	0.326
<i>Evening shift</i>				
Variable	Week 1 index	Week 4 index	<i>t</i> -test value	<i>P</i> -value (1-tailed)
How long resident took to fall asleep (Latency)	4.47	3.86	1.280	0.117
How often resident awoke	3.39	3.36	0.047	0.482
How long resident was awake	4.23	4.04	0.290	0.389
<i>Night shift</i>				
Variable	Week 1 index	Week 4 index	<i>t</i> -test value	<i>P</i> -value (1-tailed)
How long resident took to fall asleep (Latency)	1.03	1.17	0.305	0.384
How long resident actually slept	6.24	6.24	0.008	0.497
How often resident awoke*	1.66	1.96	1.203	0.132
How long resident was awake*	1.16	1.85	0.986	0.177

\*  $n = 9$



Table 2

Comparison of levels of agitation at baseline and at week 4 of melatonin administration via paired *t*-tests of CMAI Index (*n* = 10).

<i>Day shift</i>				
Variable	Week 1 index	Week 4 index	<i>t</i> -test value	<i>P</i> -value (1-tailed)
Pnab*	2.0500	1.8517	1.407	0.097
Pag**	1.4550	1.1150	1.738	0.058
Vnab***	2.3600	2.1350	1.886	0.046
Vag****	1.8200	1.5216	2.216	0.027
<i>Evening shift</i>				
Variable	Week 1 index	Week 4 index	<i>t</i> -test value	<i>P</i> -value (1-tailed)
Pnab*	1.9250	1.4633	2.338	0.022
Pag**	1.2000	1.0000	1.809	0.052
Vnab***	2.3000	1.7483	2.201	0.028
Vag****	1.5617	1.3967	0.858	0.207
<i>Night shift</i>				
Variable	Week 1 index	Week 4 index	<i>t</i> -test value	<i>P</i> -value (1-tailed)
Pnab*	1.4817	1.0200	2.663	0.013
Pag**	1.0200	1.0200	0.000	0.500
Vnab***	1.4133	1.1117	1.370	0.102
Vag****	1.2000	1.1617	0.260	0.401

\* pnab, physically nonaggressive behavior

\*\* pag, physically aggressive behavior

\*\*\* vnab, verbally nonaggressive behavior

\*\*\*\* vag, verbally aggressive behavior (*n* = 10) all *t*-tests excluded participant number 10, as they only completed through week 3 of the study

Contrary to our expectations, changes in sleep behaviors were not statistically significant during the evening and night shifts, but were statistically significant during the daytime shift. There are several possible explanations for this finding. It is obvious that daytime staff have much more contact with residents and it is possible that this contact allows them to provide a more accurate rating of the amount of sleep during their shift. Given the short half-life of melatonin, the main anticipated effect was related to decreased latency in the evening shift. Latency did show a decrease in the anticipated direction, but it was not statistically significant. Utilization of more accurate sleep assessments (e.g., wrist actigraphy) and a larger sample are needed in order to elucidate whether the administration of melatonin has a significant effect on evening and night sleep in this population.

The effect of melatonin administration on agitation is promising. Decreased agitation scores were noted in all shifts and for all types of agitation. Our results support the hypothesis that agitation is, in part, related to sleep quality and may be increased by fatigue. Therefore, the decrease in fatigue which supposedly occurred because of improved night sleep due to melatonin (albeit undocumented improved sleep), might have resulted in decreased levels of agitation. The alternative hypothesis, according to which agitation would increase during the daytime because of increased opportunities resulting from increased time awake, was rejected. Al-

though results do suggest increased time awake during daytime, this time was accompanied by decreased levels of agitation.

There was much variability among residents in their response to the melatonin. One resident seemed to have an immediate response to melatonin, with a significant decrease in latency during the evening shift (average ratings of: 6.0, 5.4, 3.8, 3.6, during the baseline and ensuing weeks, respectively). The number of hours asleep during the night shift also increased significantly (average ratings of: 4.4, 5.8, 7.5, 6.3, for baseline and 3 weeks of melatonin treatment). Similarly, the levels of agitation decreased. In contrast, another resident did not show any decrease in latency, nor consistent changes in the number of hours asleep during the night shift. Although there were some decreases in physical types of agitation during the daytime shift, there were no overall consistent changes in the manifestation of agitation in that resident.

Several limitations of the study need to be explicitly stated. Obviously, the study is limited in its scientific merit by being an open label trial rather than a double-blind placebo controlled study. Mitigating this limitation is the fact that staff members continued to assess agitation for the full 4 weeks. A placebo effect is more likely to be evident during the 1st week and decline by the 4th week, yet effects seemed to be manifested at the 4 week assessment. The study is also limited by the small number of participants, reducing both the power of the study to obtain significant results and its generalizability. Sleep ratings by staff are far from being the ideal objective method for sleep assessment. Monitoring residents every 2 h may not provide sufficiently accurate data for the type of sleep assessment required, which is supposed to characterize the sleep of a resident within a given night. On the other hand, if the normal melatonin output profile is disrupted in these patients, 3 weeks of melatonin therapy may not suffice to reset their circadian rhythm to the normal day/night cycle.

In contrast to sleep, assessment of agitation is likely to be more accurate, because physically nonaggressive behaviors are most frequently manifested (e.g., pacing in the corridors) where staff members are likely to encounter them. Similarly, verbal and vocal agitation is heard even without a specific inspection of a resident.

Improvement of sleep for nursing home residents is essential for improving their quality of life. To the extent that their agitation is a manifestation of discomfort resulting from fatigue, improvement of such fatigue and on the ensuing agitation is of major significance to their well-being. Beyond the direct suffering of the elderly patients themselves, sleep problems pose major burden to caregivers—both formal and informal. For family caregivers caring for an older person at home, sleep problems associated with agitation may impose such an impact on their daily lives, that they may be forced to seek institutionalization for the older person. Any alleviation of the evening/night-time agitation will decrease the burden for caregivers and, when applied in the community, may also decrease institutionalization.

We recognize that no accurate decisive conclusion can be drawn from our present results. A larger, double blind placebo-controlled study for a longer period of time and preferable with controlled release melatonin is necessary in order to examine

the impact of melatonin on agitated behaviors. We do believe that the results obtained in this study provide sufficient evidence to warrant such a study.

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