Cognitive Effects of Exogenous Melatonin Administration in Elderly Persons

A Pilot Study

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Objective: *Given that circadian rhythm disruption is associated with impairments in cognitive performance similar to those found in age-related cognitive decline, the authors investigated whether exogenous melatonin administration would improve cognitive functioning in healthy elderly subjects.* **Methods:** *This double-blind, placebo-controlled pilot study assigned 26 healthy elderly subjects to receive either melatonin 1 mg or placebo nightly for 4 weeks. Participants completed a sleep questionnaire and a battery of cognitive tests at baseline and at 4 weeks.* **Results:** *Melatonin administration improved reported morning "restedness" and sleep latency after nocturnal awakening, and also improved scores on the California Verbal Learning Test-interference subtest.* **Conclusions:** *Melatonin administration at a dose of 1 mg nightly may be effective in improving certain aspects of cognitive functioning and subjective reports of sleep quality in elderly subjects. It may prove to be a useful therapeutic agent in the treatment of age-related cognitive decline.*
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Age-related cognitive decline (ARCD) is defined in *DSM-IV* as an objectively-identified decline in cognitive functioning consequent to the aging process that is within normal limits, given the person's age, after it has been determined that the cognitive impairment is not attributable to a specific mental disorder or neurological condition.[1] ARCD describes the impairments in cognitive functioning that correspond to the normal aging process and that are different from the mostly fixed cognitive deficits found in the dementing illnesses. Decrements found in ARCD are generally related to mental-processing speed, verbal and nonverbal memory function involving impairment of both encoding and retrieval processes, complex problem-solving, planning, and mental flexibility or fluidity.[2] These findings have also been described in the literature using the term "age-associated memory impairment" (AAMI).[3]

Endogenous melatonin levels follow a circadian pattern, and the presence of melatonin in the central nervous system nocturnally may be a significant factor in promoting normal restorative sleep.[4] In humans, melatonin levels reach a peak in childhood, then fall during puberty and fall further during adulthood, declining steadily with age until barely detectable in elderly persons.[5] Because of its multiple biologic effects, the decrease in melatonin has also been considered as having a role in aging and age-related disease, rather than being just a consequence of aging. Over one-half of individuals over age 65 complain of sleep disorders. Although studies have shown that melatonin is not effective for sleep among elderly persons with dementia and age-related insomnia,[6,7] at least three placebo-controlled studies have reported on melatonin's efficacy as a hypnotic agent in healthy elderly subjects.[4] The effects of exogenous, administered melatonin, in doses ranging from 0.5 mg to 5 mg, have been shown, in some studies, to have measurable effects along various biological markers in individuals, effects such as phase-shifting of circadian rhythms, temperature lowering, hormonal secretion, and quality of sleep.[4,8]

Disruption of circadian rhythms may decrease cognitive performance, as shown by studies involving jet-lag or shift-work. Military personnel deployed through time-zone changes performed better on a vigilance task when they were given melatonin.[9] This information suggests that, in an age-group known for

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decreased melatonin levels, abnormal sleep patterns, and impaired cognitive functioning, exogenously administered melatonin may improve cognitive functioning by improvements in the areas of new-memory acquisition, encoding, and retrieval, and mental-processing speed. These improvements may derive either through the resynchronization of the circadian rhythm or through a direct beneficial action of melatonin upon the brain. In one placebo-controlled crossover study of 10 elderly subjects with mild cognitive impairment, treatment with 6 mg of melatonin led to improved sleep quality, mood, and delayed recall, but with no improvement in executive functions.[10] A single-case, double-blind, placebo-controlled study indicated that melatonin levels had no direct effect on cognition. However, with the temperature trough following melatonin ingestion, there appeared to be a decrease in some of the executive functions.[11]

The purpose of the pilot study was to examine whether exogenously-administered melatonin, either through synchronization of circadian rhythms, or via direct neurophysiologic action, can improve cognitive functioning in healthy elderly persons. We hypothesized that 1) Exogenously-administered melatonin at a dose of 1 mg given nightly will improve bedtime regularity, quality of sleep, and morning "restedness" in elderly persons; and 2) Exogenously-administered melatonin will improve executive functioning, memory, and mental-processing speed in elderly subjects.

METHODS

Design

The design of this pilot study was a double-blind, placebo-controlled, clinical trial, in which participants were randomly assigned, using block randomization, to receive a nightly dose of either commercially available (Schiff brand) melatonin 1 mg or placebo. The placebo capsule, prepared by the principal investigator under the supervision of the hospital pharmacist, was identical to melatonin in appearance, taste, and smell. The 1-mg dose of melatonin was chosen on the basis of a literature review of the commonly used doses for inducing sleep without producing daytime somnolence.[8]

Protocol

Thirty participants between the ages of 64 to 89 years were recruited via newspaper and flyers at a retirement home in Honolulu, Hawaii. They were told they would be participating in a study that attempts to examine whether melatonin has any effect on speed or quality of mental abilities. Participants were required to be in good medical health and without a history of dementia.

Potential participants who responded were initially screened over the phone to rule out psychiatric disorders, unstable medical problems, obvious cognitive problems, and use of psychotropic drugs. At the initial session, the project was explained, and written informed consent was obtained. Participants were interviewed and given baseline cognitive testing, and demographic information was collected. They were given either placebo or melatonin and instructed to take 1 capsule each night at approximately 8 P.M. After 1 month, participants returned for their follow-up interview and Version 2 of the cognitive testing. They were also given an exit-interview to assess for side effects, subjective reactions to the medication, and overall placebo effect. Cognitive testing was performed in the afternoon by the same examiner each time. Participants were phoned approximately midway through the study to ensure compliance.

Instruments

Baseline. Eleven demographic variables were measured at baseline: age, sex, ethnicity, occupation, marital status, education, medical condition, number of medications, aspirin use, use of Ginkgo biloba, and amount of vitamin supplementation.

Sleep. The sleep interview contained specific questions about sleep the previous day: time spent napping, total hours spent sleeping, time to fall asleep, number of nocturnal awakenings, time to fall back asleep after nocturnal awakening, early morning awakening, and morning restedness, on a scale of 1 to 5.

The sleep questionnaire contained a 21-item inventory[12] measuring seven factors related to sleep: quality and latency, depth (lightness), dream recall, negative-affect dreaming, difficulty awakening, and sleep irregularity. These items were subjectively assessed by the participants with a 6-point scale.

Cognitive assessment. Neurocognitive assessment focused on five broad areas of functioning that are understood to be affected by age-related cognitive decline.[2] The tests used are standard tests of the different cognitive functions being tested:[13] 1) executive functioning and mental flexibility, as measured by the Stroop Color Naming Test; 2) verbal memory and speed of verbal cognition, as measured by the California Verbal Learning Test (CLVT); 3) nonverbal memory and speed of cognition, as measured by the Visual Reproduction Test subportion of the Wechsler Memory Scale–Revised (WMS–R); 4) motor and mental processing speed, as measured by Finger-Tapping; and 5) short-term memory, attention, and concentration, as measured by the Digit Span Test, a component of the Wechsler Adult Intelligence Scale–Revised (WAIS–R) and WMS-R.

Exit interview. Inquiry was made as to the presence of headache; altered taste; changes in libido, mood, or energy; subjective improvements in mental abilities; changes in sleep or evening drowsiness; attitudes toward taking melatonin in the future; and, overall, whether or not they believed they were on placebo or active medication. Also, any spontaneous comments were noted.

Statistical Analysis

Descriptive and nonparametric statistics were used to compare groups. We used a nonparametric version of the *t*-test, whereby data are converted to ranks, the Mann-Whitney *U* test. Comparisons were made at baseline for demographic variables, at 1 month for the exit interview responses, and the calculated difference from baseline to 1 month for the sleep interview, sleep questionnaire, and cognitive testing scores between melatonin and placebo groups. The alpha level was set at 0.05 for significance.

RESULTS

Four participants were excluded from the study after baseline testing revealed evidence of dementia in two subjects, and interviews established that two subjects had ingested benzodiazepines within the study period. The final study group contained 26 participants, 14 in the melatonin group and 12 in the placebo group. There were no statistically significant differences in demographics between the groups.

Findings for sleep and cognition at $p \leq 0.10$ are shown in Table 1. The melatonin group scored higher on the scale of morning restedness. The melatonin group showed only slight improvement in comparison to the placebo group on all other reported measures of sleep quality, except for number of nocturnal awakenings, but these differences did not attain statistical significance. The melatonin group showed slight, but not significant, decreases in sleep irregularity, sleep needs, difficulty awakening, and negative-affect dreaming. There were no differences between groups regarding lightness of sleep and improvement in sleep quality and latency.

The melatonin group improved significantly on the CVLT Delayed and Interference portions. These differences in the melatonin group were greater recall of 1.6 and 2.6 words, respectively. This represents a clinically important difference in recall. The results on the other cognitive tests showed slight, nonsignificant improvements in the melatonin group relative to placebo, with the exception of the Delay portion of the Visual Reproduction and the Stroop Color/Word Interference and Interference Index scores.

Given the consistent direction of change in scores by the melatonin group, a-posteriori trend analysis was conducted. In this analysis, the total numbers of positive changes were compared with negative changes in scores for sleep and cognition. Significant overall improvements were detected in sleep measures and cognitive testing among the melatonin group when compared with placebo ($\chi^2_{[1]} = 11.93$; $p < 0.001$; $\chi^2_{[1]} = 3.94$; $p = 0.047$, respectively).

On the exit interview, the placebo group subjectively reported significantly greater improvements in their sleep ($U = 44.5$; $p = 0.04$). There were no differences in evening sleepiness, headaches, attitude toward taking melatonin in the future, and overall belief that they were taking active medication.

DISCUSSION

The limitations of the study include the following: 1) sample size was small; 2) serum melatonin levels were not measured; 3) the study was of relatively short duration; and 4) sleep parameters were self-re-

ported. However, the findings provide some insight into potential benefits of melatonin on sleep and cognition in elderly persons. It should be emphasized that these findings may not be generalizable to elderly persons with dementia.

Exogenous melatonin has been shown to be effective in promoting sleep initiation, sleep maintenance, and overall sleep efficiency in elderly insomniac patients.[8] Our findings that exogenous melatonin at 1 mg nightly appeared effective in improving morning restedness supports previous data. The instruments used to measure sleep quality in our study relied upon subjective report. We found, however, that the placebo group reported greater improvement in sleep quality. This raises the possibility of placebo effects on subjective sleep quality, and expectancy effects in clinical trials. The expectancy that melatonin will be effective has been shown to be a factor in subjective sleep experience.[14] Our findings ought to be replicated using more objective measures such as wrist actigraph and sleep journal entries.

Our findings that melatonin administration was related to improvement on two measures of cognitive functioning suggest the possibility that the cognitive decline in elderly persons may, at least in part, be secondary to a decline in melatonin with age. Our study demonstrated that exogenous melatonin administration may increase cognitive performance to a noticeable and clinically important degree in elderly persons without dementia: they showed increased shopping-list recall by 2 items of a 16-item list, and increased reverse digit-span recall by 1 digit. Therefore, some of the elements of cognitive decline in elderly persons, including age-related cognitive decline, may be effectively treated with melatonin administration.

Our study does not identify the mechanism of action of the beneficial effects of melatonin upon cognitive functioning. It is interesting to note that the improvements in cognitive functioning were not accounted for by the improvements in sleep. This finding suggests that, in addition to improving circadian functioning, melatonin may exert a directly beneficial physiologic effect upon the brain. Further study would be needed to investigate this.

CONCLUSION

Although this pilot study showed few statistically significant findings, the sleep-quality and cognitive changes detected are intriguing. Exogenous melatonin is potentially effective as a hypnotic agent and may improve restedness and some measures of sleep quality at a dose of 1 mg nightly. Exogenous melatonin administration may be of potential benefit in the treatment of age-related cognitive decline in healthy elderly persons. The demonstrated improvements in cognitive functioning were not accounted for by improvements in sleep alone, thus providing indirect evidence that melatonin may exert a directly beneficial physiological effect upon the brain. Age-related cognitive decline may relate to circadian-rhythm disturbance, suggesting a functional lack of endogenous melatonin. Further investigation should address this question.

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TABLE 1. Mean, standard deviation, median, and *U* scores for sleep and cognitive measures at Baseline and 1 month for melatonin and placebo groups, mean (standard deviation)/median

	Baseline		One Month		
	Melatonin	Placebo	Melatonin	Placebo	*U* (p)
Morning restedness	4.1 (1.1) 4	4.1 (1.1) 4	4.6 (0.5) 5	3.6 (1.4) 4	42 (0.04)
Sleep latency after nocturnal awakening, minutes	15.2 (31.5) 4.5	10.8 (26.4) 2	8.8 (23.7) 1	12.1 (26.7) 1.5	43.5 (0.06)
Dream recall and vividness	3.4 (1.0) 3.3	2.8 (1.1) 3	3.2 (0.9) 3.5	3.1 (1.2) 3	47.5 (0.10)
CVLT: recall after interference	8.4 (2.9) 8	10.4 (2.8) 11	9.3 (3.3) 9	8.6 (3.5) 8	35.5 (0.02)
CVLT: recall after delay	8.1 (1.7) 8	10.3 (3.3) 11	8.9 (3.1) 9	9.4 (3.0) 9	46.5 (0.08)

Note: CVLT: California Verbal Learning Test.

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