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Does melatonin improve sleep in older people? A randomised crossover trial

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Abstract

Study objective: to determine whether melatonin will improve quality of sleep in healthy older people with age-related sleep maintenance problems.
Design: a double blind randomised placebo controlled crossover trial in healthy older volunteers.
Setting: a largely urban population, Auckland, New Zealand.
Participants: participants were part of the larger Possible Role of Melatonin in Sleep of Elders study. People 65 years or more of age were recruited through widespread advertising. We screened 414 potential participants by mail using the Pittsburgh Sleep Quality Index, and selected 194 for clinic interview. Exclusions included depression, cognitive impairment, hypnosedative medications, sleep phase abnormalities, medical and/or environmental problems that might impair sleep. Twenty normal and 20 problem sleepers were randomly allocated for this study from a larger sample of 60 normal and 60 problem sleepers.
Measurements and results: 24-hour urine 6-sulphatoxymelatonin was measured to estimate melatonin secretion in each participant. Five milligrams of melatonin, or matching placebo were each taken at bedtime for 4 weeks, separated by a 4-week washout period. Sleep quality was measured using sleep diaries, the Leeds Sleep Evaluation Questionnaire, and actigraphy. There was a significant difference between the groups in self-reported sleep quality indicators at entry, but no difference in melatonin secretion. Melatonin did not significantly improve any sleep parameter measured in either group.
Conclusion: 5 mg of fast release melatonin taken at bedtime does not improve the quality of sleep in older people with age-related sleep maintenance problems.

Keywords: *melatonin, 6-sulphatoxymelatonin, sleep, elderly, older people*

Introduction

Sleep disturbances in older people have been extensively reviewed [1–5]. Older people experience more frequent nocturnal arousals, earlier bedtime and wake-up times, increased daytime napping, and tend to be less tolerant of phase shifts of the sleep-wake cycle. It is generally accepted that time in bed increases, but total sleep time is either reduced or unchanged; thus sleep efficiency is reduced, sleep latency is normal or increased, and wake time after sleep onset is increased.

Melatonin (5-methoxy-*N*-acetyltryptamine) is a lipid soluble hormone secreted by the pineal gland during the hours of darkness. Under normal day-night routines melatonin rhythms have been shown to be very stable [6, 7] but 24-hour secretion is significantly reduced with age [8–12]. When melatonin is administered orally, intranasally, or intravenously to young volunteers, mild sedation occurs [13]. In some studies melatonin was administered in very high doses during daytime, but later polysomnographic studies led to speculation that endogenous melatonin may play a role in sleep onset and maintenance. Low or absent melatonin levels in older people have been linked not only to sleep disorders but also with longevity, which may in part be the reason why this hormone is consumed nightly by millions of people [14]. Yet there is limited evidence as to a useful hypnosedative role for melatonin in sleep problems of healthy older people, no evidence of an anti-ageing effect, and no information on long-term side effects.

Three small non-randomised studies of older people with insomnia, including some with chronic illness, have reported that 2 mg or 3 mg sustained release preparations of melatonin were effective for sleep maintenance, measured by sleep diaries and actigraphy [15–17]. However, a placebo-controlled, double blind, crossover trial of early, continuous, and late melatonin delivery strategies for healthy people with insomnia aged 55–80 years, using polysomnography, actigraphy, and sleep diaries, showed that melatonin was not effective in maintaining sleep, although sleep latency to persistent sleep was reduced [18].

Our research null hypothesis stated that oral melatonin taken at bedtime would not improve sleep either in older people with age-related sleep maintenance problems, or in older people reporting normal sleep. The study was approved by the Ethics Committee of North Health, the Northern Region of the Health Funding Authority of New Zealand, and by the Standing Committee on Therapeutic Trials, Department of Health.

Methods

Recruitment and screening

Recruitment and screening for the Possible Role of Melatonin in Sleep of Elders (PROMISE) study has been reported in detail elsewhere [19]. In brief, participants were recruited from a largely urban area of Auckland, New Zealand. Potential participants underwent an initial verbal interview and if they seemed suitable were sent the Pittsburgh Sleep Quality Index (PSQI) [20, 21] questionnaire to be completed and returned by mail. Participants eligible on the basis of their PSQI scores attended a clinic interview where screening followed standard protocols including the Mini Mental Status Examination (MMSE) [22] and the Geriatric Depression Score (GDS) [23]. A medical practitioner reviewed responses to the screening questionnaire, and elicited in detail any health issues which might interfere with sleep. Classification as normal sleeper, or age-related sleep maintenance problems ('problem sleeper') was a clinical decision made at interview following discussions based on reported features of sleep patterns, for example sleep latency, numbers of awakenings, and deterioration in sleep quality after reaching 50 years of age.

Sixty normal sleepers, 60 problem sleepers, and 20 with phase advanced sleep syndrome were found for the PROMISE study. One third of the normal and problem sleeper group were randomly selected for the trial of melatonin or placebo reported here.

Exclusion criteria

Age under 65 years; below 26 (out of 30) points on the MMSE; a score of >6 on the GDS (depression can be a cause of sleep disturbance [2, 5]); sleep problems not age related [24]; advanced or delayed sleep phase syndrome; poor sleep hygiene; medical conditions significantly interfering with sleep (including sleep apnoea); changes in medication during the study; use of hypnosedatives; creatinine clearance <0.41 ml/s (6-sulphatoxymelatonin excretion is validated as an estimate of melatonin secretion only for clearances above this value [25]).

Measurement of melatonin secretion

Melatonin secretion was estimated by measuring its principal metabolite, 6-sulphatoxymelatonin, in a 24-hour collection of urine from each subject [19], measured by radioimmunoassay [26].

Double blind randomised controlled crossover trial of melatonin or placebo

Participants were given 5 mg capsules of melatonin (melatonin in a gelatine capsule), or placebo (glucose in an identical gelatine capsule) and instructed to take the preparation on retiring to bed. Adverse reactions were monitored by way of a 24-hour hotline, regular telephone checks, and recorded in a diary. Protocol allowed for withdrawal if a serious side effect was suspected.

The sequence of treatments was determined by a computer-generated random process, stratified by sleep group. All investigators and study staff, except one (JD), were blinded as to the order of the ingredient trialed. At the end of each trial month, containers were returned and any unused capsules recorded.

Melatonin or placebo capsules were each taken for 4 weeks, separated by a 4-week washout period. If protocol violation occurred the participant was either withdrawn from the study, or the trial for that participant was recommenced after a further 4-week washout period, using the same sequence of melatonin and placebo.

Measurement of sleep quality indicators

Sleep diaries were completed by each participant over both entire 4 week treatment periods. Sleep diaries included the Leeds Sleep Evaluation Questionnaire [27] and an evening section in which participants recorded any daytime naps, time to bed, and time of lights out before sleep. A morning section recorded perceived time to sleep, wake up and final get up times, and periods of wakefulness during the night. The Leeds Sleep Evaluation Questionnaire uses a 10 cm visual analogue scale to identify perception of quality of sleep after each night. Actigraphy was undertaken for 5 consecutive days in the last week of each trial period. Actiwatches (actigraphs), purchased from Cambridge Neurotechnology Ltd, UK, were allocated according to a rotation protocol to ensure that the same actigraph was used for each participant. Actiwatches record 24-hour motor activity summarised on a prespecified time basis by the 'Sleepwatch' software, validated against polysomnography

[28, 29]. Participants wore their actiwatches on the non-dominant wrist. Actiwatches were set to record motor activity every 30 seconds, low activity suggests undisturbed or relatively undisturbed sleep. From this data the software program measures a large number of sleep parameters including sleep latency (time to sleep), sleep duration, number of awakenings, and sleep efficiency.

Main sleep outcomes

Sleep quality measures were chosen a priori: sleep duration (minutes), sleep latency (minutes), number of awakenings, sleep efficiency (time asleep/time in bed (lights out to final get up)).

Power and sample size

Sample size calculations were based on clinically relevant changes in problem sleepers, with estimates obtained from an earlier pilot study and from available literature. A 15 min change in sleep latency, a 6% absolute change in sleep efficiency, or a 0.6 change in number of awakenings would require 12 participants in each group (with $\alpha = 0.05$ and power = 80%). It was decided to recruit 20 participants to allow for drop-out.

Statistical analysis

Management and statistical analyses were conducted using SAS Versions 8.02 [30] and S-PLUS 2000 Professional Edition [31]. Due to the small sample sizes and skewed nature of the data, medians of the baseline demographic and sleep quality indicators are reported, with their 95% confidence intervals (CI). For the trial data the mean value of each of the seven sleep variables for each participant were calculated while on melatonin or placebo. A treatment effect for each participant was calculated as being the difference between their means. For each group and each measure, the medians under each treatment and median treatment effect were obtained. Confidence intervals for the medians were calculated via bootstrapping with resampling for each person within each treatment. More complex analyses were undertaken to account for the correlations between repeated measurements on each individual and for potential confounding factors. Mixed models were used for those variables that appeared normally distributed, generalised mixed models for those variables which were non-normal (i.e. count data). For data that fitted neither category the data was transformed to approximate normality. The comparison of differences in treatment effects between high and low secretors was performed using a two-sided exact Wilcoxon test.

Results

Figure 1 illustrates the progression of participants throughout the three PROMISE studies, and the main

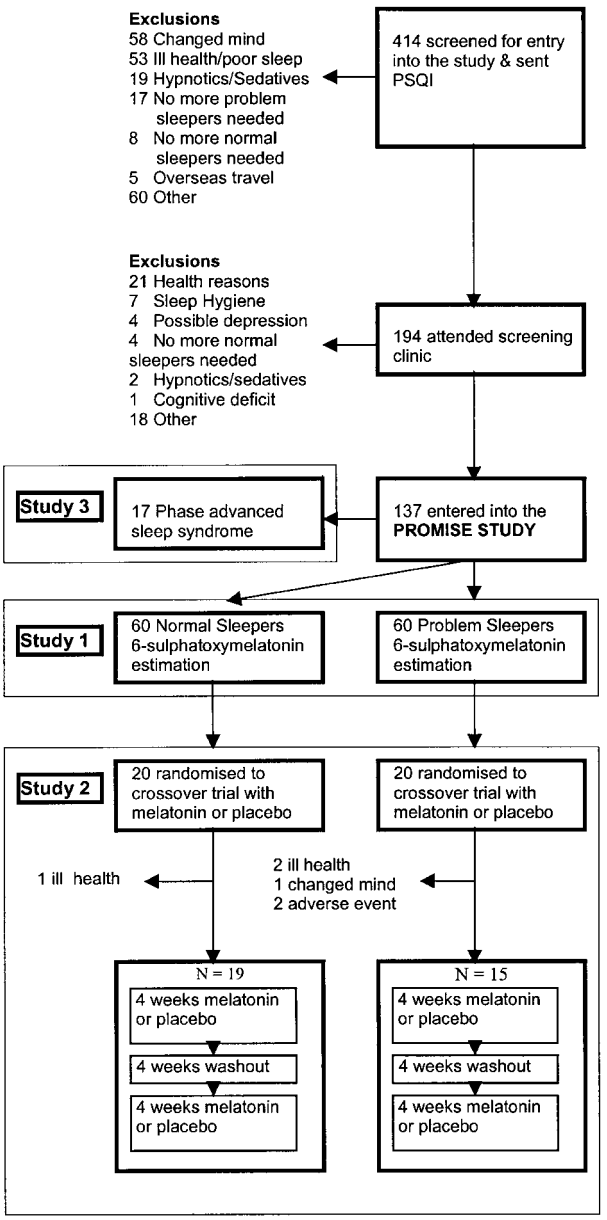

Figure 1. PROMISE study flowchart. Results from Study 2 are reported in this paper.

reasons for exclusion. Study two is described in this paper. One hundred and ninety-four people attended the screening clinic, and 20 from each group of 60 normal and 60 problem sleepers were randomly allocated to the double blind crossover trial of supplementary melatonin or placebo. Of these 19 normal, and 15 problem sleepers completed the study.

The main reasons for dropping out are shown in Figure 1. Very few side effects were reported but one subject reported excessive drowsiness on both melatonin and placebo within a few days of commencement of each treatment period, and was withdrawn. Analysis of capsules from each study period confirmed that placebo and melatonin treatments had been supplied as per

protocol. A second person was withdrawn after excessive drowsiness in the first 2 days of the second phase of the study. When the codes were checked, this person had commenced melatonin at this time, and had been symptom free on placebo during the first month of the trial. Three more withdrew because health problems required hospitalisation: bowel obstruction, unstable angina, and cellulitis. These conditions were not thought to be related to melatonin. A sixth person changed their mind about continuing in the study after randomisation.

Table 1 shows baseline characteristics. There were no important differences in age, sex, caffeine and alcohol intake, or medications between the groups. The overall mean age in the study was 71.7 years (SD 4.9), 68% of participants were women. Median 24-hour 6-sulphatoxymelatonin levels were not statistically different, in normal sleepers 6.3 μg (95% CI 5.6, 9.20), and in problem sleepers 8.8 μg (6.7, 15.7) ($P=0.26$).

Table 2 shows the self reported sleep quality indicators recorded at clinic interview. The self reported median sleep time for the problem sleeper group was 5 h 40 min, much less than that reported by normal sleepers (7 h 25 min, $P<0.001$). Reported sleep efficiency was also lower, 69% *vs* 91% ($P<0.001$).

Table 3 compares median differences in sleep diary and actigraphy measured sleep quality indicators between the melatonin and placebo arms, with 95% CIs. The lack of a significant effect of melatonin on the seven measured sleep parameters was consistent between normal sleepers and problem sleepers. Of the seven measures of sleep quality listed in Table 3 only the number of awakenings in normal sleepers, measured by actigraphy, showed a significant response to melatonin where the median decrease was 4.4. Repeated measures models gave similar results except for awakenings, where normal sleepers showed a non-significant decrease ($P=0.08$). In no other result was any effect of melatonin apparent on sleep duration or quality. When all low melatonin secretors (those below the median), and high secretors (those above the median), were compared regardless of sleep category, no difference in treatment effect between the groups was found. Examination of bootstrapped standard deviations of the median differences in sleep quality indicators taken from diary records showed they were each slightly less than the standard deviations estimated prior to the trial. This indicates that there was sufficient power to detect the hypothesised changes.

Table 1. Baseline characteristics of subjects by Sleep Group

	Normal sleepers ($n=20$)	Sleep maintenance problems ($n=20$)
	n	*n*
Sex		
Female	16	10
Male	4	10
Age		
65–69	7	5
70–74	7	10
75–79	3	2
80–84	3	3
Body mass index		
Underweight (<20)	0	1
Normal (20–24)	9	6
Overweight (25–29)	7	9
Obese (30+)	4	4
Caffeine after 6 pm[a]		
Yes	14	8
No	6	12
Alcohol (g/day)		
0–10	7	8
11–20	2	4
>20	2	3
Non/occasional drinker	9	5
Medications		
Antihypertensives	1	0
Betablockers	4	4
Antiepileptics	0	2
People on medications	5	6

[a]Caffeine from tea or coffee.
No significant differences between groups.

Discussion

This double blind randomised control trial of placebo or melatonin has shown that a fast release capsule containing 5 mg melatonin, taken at bedtime, does not have any useful role in maintaining sleep in older people with sleep maintenance problems, or any effect on sleep

Table 2. Self-reported baseline sleep quality indicators derived at entry

	Normal sleepers ($n=20$)		Sleep maintenance problems ($n=20$)		
	Median	95% CI	Median	95% CI	*P*-value[a]
Sleep quality measures					
PSQI (5 or less=normal sleep)	4	(3–5)	10	(8–11)	<0.0001
Time in bed (minutes)	495	(465–510)	510	(480–555)	0.25
Sleep time (minutes)	443 (7 h 25 min)	(410–460)	340 (5 h 40 min)	(290–400)	<0.001
Sleep latency (minutes)	10	(5–15)	10	(10–20)	0.17
Number of wakenings	1	(1–2)	2	(1–2)	0.02
Sleep efficiency (%)[b]	91	(86–93)	69	(55–77)	<0.0001

[a]Between group comparisons.
[b]Sleep efficiency=time asleep/time in bed (lights out to get up).

Table 3. Medians of the participants' mean measures of sleep characteristics, on active and placebo treatment, and the median difference in their participant's means, for normal and problem sleepers (*denotes significant difference)

	Active phase	Placebo phase	Difference
Normal sleepers ($n=19$)			
Actigraphy			
Latency (minutes)	2.6 (1.0, 4.2)	5.2 (1.2, 5.6)	−1.2 (−2.6, 1.6)
Sleep time (hours)	7.3 (7.2, 7.5)	7.3 (7.0, 7.5)	0.14 (−0.16, 0.33)
Awakenings (*n*)	36.4 (30.4, 38.2)	40.2 (34.4, 41.2)	−4.4 (−7.0, −1.0)*
Sleep efficiency (%)	86.4 (84.9, 88.3)	87.1 (86.1, 87.8)	1.48 (−0.60, 2.34)
Diary			
Diary wakenings (*n*)	1.9 (1.7, 2.0)	1.8 (1.4, 1.9)	0.04 (−0.14, 0.14)
Quality scale	5.3 (5.1, 5.5)	5.0 (4.9, 5.2)	0.25 (−0.04, 0.42)
Alertness scale	5.0 (4.9, 5.1)	4.8 (4.7, 5.0)	0.12 (−0.04, 0.26)
Problem sleepers ($n=15$)			
Actigraphy			
Latency (minutes)	1.6 (0.6, 2.8)	1.4 (0.4, 2.0)	0.0 (−0.8, 1.4)
Sleep time (hours)	7.3 (7.2, 7.6)	7.4 (7.0, 7.8)	−0.18 (−0.44, 0.23)
Awakenings (*n*)	41.2 (36.0, 45.2)	40.2 (34.6, 43.6)	−0.6 (−4.8, 4.0)
Sleep efficiency (%)	84.1 (83.8, 86.3)	86.2 (84.9, 87.1)	0.06 (−1.50, 1.66)
Diary			
Diary wakenings (*n*)	1.7 (1.5, 2.1)	1.8 (1.5, 2.0)	0.12 (−0.13, 0.26)
Quality scale	5.7 (5.3, 5.8)	5.4 (5.2, 5.7)	0.01 (−0.29, 0.31)
Alertness scale	4.8 (4.6, 5.1)	5.0 (4.8, 5.2)	0.00 (−0.28, 0.16)

latency. Nor was there any difference in the way low and high secretors responded to treatment, regardless of sleep category. These results agree with a similar study published after our research had commenced [18]. Our results did show a significant reduction in awakenings recorded by actigraphy but only in normal sleepers taking melatonin, and not the age-related sleep maintenance problem group. We believe that this was a chance finding since it is inconsistent with all other results. Actigraphy records between 30 and 50 events as 'awakenings' during sleep, at a time when the participant may have recalled waking only two or three times.

Our choice of melatonin preparation was restricted by difficulty in obtaining details on the pharmacodynamic and pharmacokinetic profile of the product from manufacturers. Discussion on this problem has been published since the commencement of our study [32, 33]. Our intention was to use a sustained release product which would mimic, as far as possible, the physiological timing of normal melatonin secretion. However, because validation data was difficult to obtain, we elected instead to use an immediate release product, 5 mg melatonin dispersed in lactose in a gelatine capsule. When ingested by a younger group of people a similar 2 mg capsule has been shown to produce peak melatonin levels of over a 100 times expected physiological levels after about 1 h, and remain high for at least 7 h [34]. Since this product does not mimic normal physiologic secretory profiles and was ingested at bedtime, the choice was not ideal and may have influenced our results.

The study was set up to simulate the situation faced by a physician who wishes to treat an older patient presenting with age related sleep maintenance problems. Problem sleepers were carefully screened to exclude any possible reason for deterioration in sleep quality other than age. People taking medications were included as long as these, and the dose, were not changed during the study period. Whilst it is recognised that some prescription drugs will suppress or enhance melatonin secretion we argued that if a low melatonin secretory profile had an influence on sleep patterns arising as a side effect of the drug, then supplementary melatonin should demonstrate significant improvement.

We chose to use sleep diaries and actigraphy with which to measure key treatment effect outcomes. Many problem sleepers were sure that they did not sleep more than 4–5 hours after sleep onset, although during the trial diaries and actigraphy suggested that they probably slept longer than this, whether taking placebo or melatonin. This could be due to a placebo effect of both preparations, though sleep diary records suggested that participants felt that sleep quality had not altered significantly from their original perspective. With hindsight we recognise that it would have been helpful to have used diaries and actigraphy as part of the screening process.

Actigraphy [28, 29, 35–38] has been validated against polysomnography, and intrasubject variability of activity and immobility measures of sleep are reported to remain stable [39]. Use of actigraphy to study insomnia in older people appears to be more sensitive to change than sleep diaries, although sleep diaries remain useful in assessing a subject's perceptions of sleep [40]. Guidelines for use of actigraphy have been produced [41] and it is recognised that the major limitation is one of precision. Nevertheless in intra-subject comparisons, using the same actigraph on the same non-dominant limb, actigraphy has proved reliable. Although no substitute for polysomnography, actigraphy has the advantages of

portability, is non-invasive, and subjects can be studied in their own environment for a long period of time.

Key points

- Melatonin, a hormone secreted at night by the pineal gland, is thought to have mild hypnosedative properties.
- Secretion of melatonin is significantly lower, sometimes absent, in older people.
- Supplementary melatonin is taken by many older people regularly to promote sleep and longevity though little evidence for benefit exists.
- This study found that a 5 mg fast release preparation of melatonin did not improve the duration or quality of sleep in people over the age of 65 years with age-related sleep maintenance problems.
- Melatonin levels were similar in people reporting normal sleep, or age-related sleep maintenance problems.

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