Melatonin in Medically Ill Patients With Insomnia: A Double-Blind, Placebo-Controlled Study

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Background: It has been suggested that melatonin improves sleep functioning, but this possibility has not been studied in medical populations.

Method: 33 medically ill persons with initial insomnia were randomly assigned to receive either melatonin (N = 18) or placebo (N = 15) in a flexible-dose regimen. Double-blind assessments of aspects of sleep functioning were obtained daily across the next 8 to 16 days.

Results: The mean stable dose of melatonin was found to be 5.4 mg. Relative to placebo, melatonin significantly hastened sleep onset, improved quality and depth of sleep, and increased sleep duration without producing drowsiness, early-morning "hangover" symptoms, or daytime adverse effects ($p < .05$). Melatonin also contributed to freshness in the morning and during the day and improved overall daytime functioning. Benefits were most apparent during the first week of treatment.

Conclusion: Melatonin may be a useful hypnotic for medically ill patients with initial insomnia, particularly those for whom conventional hypnotic drug therapy may be problematic.

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Melatonin is secreted by the pineal gland. It has been suggested that melatonin benefits a wide range of sleep disorders, particularly those that are related to disturbances of circadian rhythms; such disorders include insomnia associated with jet lag, shift work, and blindness.[1,2] Levels of melatonin are decreased in the elderly, and this may be one of the reasons why the elderly frequently experience insomnia[3]; melatonin has been found to facilitate sleep in elderly subjects as well.[4,5] Small benefits in sleep functioning have also been reported in patients with major depression receiving fluoxetine.[6] Finally, melatonin has been found to facilitate the discontinuation of benzodiazepines, possibly by attenuating withdrawal insomnia.[7]

Measures of sleep that have been suggested to improve with melatonin therapy in healthy, middle-aged subjects include the following: actual sleep time, sleep efficiency (actual sleep time as a percentage of time in bed), non–rapid eye movement (REM) sleep duration, and latency to REM sleep. The changes are small in magnitude, however, and range from 5% to 20%.[8] The preceding notwithstanding, certain studies have failed to identify sleep-related benefits with melatonin.[9,10]

Several mechanisms have been suggested that could mediate the sleep-promoting effects of melatonin. These include the correction of circadian dysregulation, the attenuation of the daytime alerting process generated by the suprachiasmatic nucleus, and the lowering of core body temperature.[1,11] Several recent reviews have examined the effects of melatonin on sleep[1,12,13] and the clinical importance of the hormone.[11,14]

For reasons related to accumulation, respiratory depression, or central nervous system suppression, benzodiazepines and other hypnotic agents are relatively contraindicated in certain medical disorders associated with insomnia; such hypnotics are associated with further disadvantages, such as the production of tolerance and dependence. These considerations suggest that it might be useful to study the sleep-inducing properties of melatonin in medically ill subjects. In patients with compromised renal or hepatic functioning, daytime levels of melatonin are increased, the nocturnal rise of melatonin is blunted, and melatonin rhythmicity is disturbed[14]; melatonin hypnosis may be particularly helpful in such patients. To the best of our knowledge, no study has evaluated the benefits and risks of melatonin in medically ill patients with insomnia. We therefore sought to conduct such a study.

METHOD

The study addressed inpatients recently admitted (April and May 1999) to the medical wards of a general

Table 1. Sample Description

Variable	Melatonin (N = 18)	Placebo (N = 15)	Significance
Age, y, mean (SD)	59.7 (11.1)	51.4 (14.2)	t = 1.89, df = 31, NS
Range, y	43–85	23–70	
Sex, N			p = .70, NS[a]
Male	14	10	
Female	4	5	
Primary diagnosis, N[b]			
Cardiovascular disease	1	2	
Cerebrovascular disease	1	0	
Hematologic disease	1	2	
Liver disease	4	2	
Gastrointestinal disease	1	0	
Pulmonary disease	7	4	
Diabetes	1	2	
Burns	1	0	
Psoriasis	0	1	
Malnutrition	1	1	
Undiagnosed	0	1	

[a]Fisher exact test.
[b]Comorbid diagnoses not specified.

hospital in Bangalore, India. The sample comprised consecutive patients with initial insomnia for whom hypnotic drug therapy was contemplated; no attempt was made to specifically recruit or screen for patients with syndromal sleep disorders. Initial insomnia was defined as sleep-onset latency that was 30 minutes or greater, that had been present for at least the past 2 weeks, and that was causing clinical distress. Eligible patients who provided informed consent in writing were randomly assigned to receive either melatonin (Aristo Pharmaceuticals Ltd., Bombay, India) or lactose placebo in identical capsules. Each melatonin capsule contained 3 mg of the hormone.

A patient-determined, flexible-dosing schedule was permitted, with certain restrictions. Patients were prescribed 1 capsule of medication each night for the first 2 nights. Thereafter, they were allowed to raise the dose by 1 capsule a night every alternate night, depending on the benefits experienced and subject to a maximum of 4 capsules a night. Downward dose titration was also permitted. Patients were instructed to take their capsule(s) with food so that melatonin bioavailability would be higher in those who were receiving the active drug. Treatment continued for a minimum of 8 days and for a maximum of 16 days and depended on the duration of the patient's stay in the hospital.

Information obtained at baseline and endpoint included the mean time taken to fall asleep during the previous 3 days, the mean number of nighttime awakenings, and the mean duration of nighttime sleep. At endpoint, patients' global ratings of overall benefit were also obtained; for this purpose, a 5-point scale was used, with higher ratings indicating greater benefit.

Patients were also assessed at baseline, daily during the course of the trial, and at endpoint using a 15-item structured questionnaire (with anchored responses) that examined various aspects of sleep functioning (Appendix 1). This questionnaire was developed by one of the authors (C.A.) and had been found satisfactory in a previous (unpublished) study of the effects of an herbal formulation on sleep functioning. The questionnaire was administered each afternoon and focused on the effects of the previous night's medication. Patients and rater alike were blind to treatment status.

Shortly before the patients' scheduled discharge from the hospital, after 8 to 16 days of treatment, drug therapy was abruptly stopped and withdrawal effects were assessed over 3 consecutive days (Appendix 2).

Statistical Methods

To reduce the number of data points, all information was pooled as follows: days 1 and 2, days 3 and 4, days 5 and 6, and so on, to days 15 and 16. Since different patients were treated for different durations, depending on their scheduled duration of stay in the hospital, the last-observation-carried-forward method was used in analysis.

The independent sample t test was used to compare means between melatonin and placebo groups; when variances were significantly heterogeneous, the t test was used with modified degrees of freedom. When distributions were significantly nonnormal, the Mann-Whitney U test (with z corrected for ties) was employed. The chi-square test was used to compare frequency distributions between groups. All tests of significance, wherever applicable, were 2-tailed. Alpha for significance was set at 0.05, but since this was an exploratory study, Bonferroni corrections were not applied, and trends ($.05 < p < .10$) were also recorded. The risk for a type I error was accepted, but was partly offset by the predominant use of nonparametric tests, which are known to be conservative.

RESULTS

During the study period, 33 eligible patients were recruited and received either melatonin (N = 18) or placebo (N = 15). The 2 groups differed little in age, sex, and clinical diagnosis (Table 1).

Twenty-one patients (melatonin N = 11; placebo N = 10) received treatment for 8 days, 8 patients (melatonin N = 5; placebo N = 3) received treatment for 10 days, and 4 patients (melatonin N = 2; placebo N = 2) received treatment for 16 days. Thus, there was little difference in the duration of treatment in the 2 groups.

The number of capsules consumed nightly increased across time (Table 2). As compared with melatonin-treated patients, placebo-treated patients consumed a significantly larger number of capsules on days 9 and 10; there was a trend for the number to be higher on days 11 and 12, as well. The mean dose of melatonin was 1.8 capsules per night from days 5 to 16; this corresponds to 5.4 mg of melatonin. The modal melatonin dose from days 5 to 16 was 2 capsules (6 mg) nightly.

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The 2 groups did not differ significantly in time to fall asleep, number of nighttime awakenings, or duration of sleep at baseline (Table 3). At endpoint, melatonin-treated patients were observed to fall asleep faster and to sleep longer than the placebo-treated patients. On global assessment, patients in the melatonin group reported significantly greater overall sleep-related benefits across the course of therapy (see Table 3).

The sleep questionnaire yielded a large quantity of information. In the interests of brevity, the results are summarized in Table 4. Melatonin made a significant positive impact ($p < .05$) on sleep latency, quality of sleep, depth of sleep, and freshness on awakening in the morning; there was also a possible positive impact ($.05 < p < .10$) on daytime freshness and on overall daytime functioning. Melatonin and placebo did not differ on the other items.

Headache on awakening was reported by 1 melatonin-treated patient on a total of 4 days; 3 placebo-treated patients reported headache on 1 day each. Heaviness in the head on awakening was reported by 3 melatonin-treated patients on 1, 2, and 3 days, respectively; 3 placebo-treated patients reported this symptom on 1 day, and 1 patient reported it on 2 days. No patient in either group reported mental dullness on awakening. All hangover-type complaints were mild and lasted for 10 to 30 minutes.

Relationships between age, dosing, and benefits were examined in the melatonin group. In comparison with younger patients (age < 60 years), older patients (age 60 years and greater) showed a trend for the consumption of a larger number of capsules between days 5 and 10; this attained statistical significance ($p < .05$) on days 11 to 16. Age, however, did not influence sleep-onset latency, number of nighttime awakenings, duration of sleep, or global rating of overall benefit at either baseline or endpoint.

No patient reported any withdrawal symptom after discontinuation of treatment. An examination of individual case records found no discernible pattern between diagnosis and response to treatment. No adverse effects associated with treatment were apparent on unstructured questioning of the patients.

Table 2. Number of Capsules Consumed Nightly[a]

Day	Melatonin (N = 18)	Placebo (N = 15)	Significance[b]
1–2	1.0 (0.0)	1.0 (0.0)	NS
3–4	1.0 (0.0)	1.0 (0.0)	NS
5–6	1.8 (0.4)	1.8 (0.4)	NS
7–8	1.8 (0.4)	1.9 (0.4)	NS
9–10[c]	1.8 (0.4)	2.1 (1.9)	z = 2.15, p = .03
11–12	1.8 (0.5)	2.1 (0.4)	z = 1.85, p = .06
13–14	1.8 (0.5)	2.1 (0.3)	NS
15–16	1.8 (0.5)	2.1 (0.3)	NS

[a]Data are presented as mean (SD).
[b]Mann-Whitney U test.
[c]The data have been rounded to the first decimal place; therefore, although the data from days 9 to 16 are similar, the statistical conclusions are different.

DISCUSSION

In consonance with the literature,[1,12,13] melatonin was observed to have a favorable impact on various aspects of sleep functioning. Melatonin hastened sleep onset without producing drowsiness; this is an asset because drowsiness associated with hypnotic drug therapy using conventional agents often works to the patient's disadvantage in cognitive and psychomotor domains. Our finding supports common opinion which holds that melatonin does not make people feel sleepy; it is necessary to actually go to bed and lie down to experience hypnosis with melatonin.

The absence of symptoms related to sedation was also exemplified by the early morning freshness experienced by melatonin-treated patients and by the freshness and better functioning they experienced during the day. These benefits probably resulted from better nighttime sleep. In contrast, many patients treated with conventional hypnotic agents experience headache, early morning dullness, heaviness of head, and other "hangover" symptoms.

Melatonin was very well tolerated and did not differ from placebo in the production of adverse effects; again, this favorable side effect profile contrasts sharply with that of conventional hypnotic drugs.[15]

It was heartening to note that the abrupt discontinuation of melatonin, 3 days before the scheduled discharge of the patients from the hospital, occasioned neither rebound insomnia nor any of 24 other symptoms that are commonly associated with drug discontinuation following conventional hypnotic drug therapy. At least in the short term, melatonin therapy is not associated with drug dependence; in contrast, a varying degree of discontinuation reaction is observed with different conventional hypnotics after even as brief a period as a week of therapy.[15]

The benefits associated with melatonin in medically ill patients, combined with a lack of adverse effects, withdrawal effects, or risk for significant drug interactions, suggest that melatonin may be a useful treatment in medically ill subjects in whom conventional hypnotic drugs cannot be used because of a risk for adverse events related to either pharmacodynamic or pharmacokinetic effects.

Melatonin treatment may be especially helpful in patients whose natural melatonin rhythms are disrupted because of compromised renal or hepatic functioning. Although we observed no specific diagnosis-related response pattern to melatonin in our very small sample, future research might do well to examine populations such as those with liver or renal disease to ascertain whether diagnosis influences response.

Most melatonin-treated patients stabilized on a dose of 2 capsules (6 mg) nightly; the mean stable dose of melatonin was 5.4 mg. Placebo-treated patients tended to consume a larger number of capsules, no doubt because they

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Table 3. Patients' Self-Reports of Sleep at Baseline and Endpoint

Variable	Melatonin (N = 18) Mean (SD)	Melatonin (N = 18) Range	Placebo (N = 15) Mean (SD)	Placebo (N = 15) Range	Significance
Time to fall asleep at baseline, h	1.4 (1.1)	0.3–3.0	1.8 (1.0)	0.2–3.0	NS
Time to fall asleep at endpoint, h	0.3 (0.2)	0.1–0.5	1.0 (1.0)	0.2–3.0	z = 1.96, p = .05
No. of nighttime awakenings at baseline	3.4 (1.2)	1–5	3.4 (0.9)	2–5	NS
No. of nighttime awakenings at endpoint	2.0 (0.8)	1–3	2.2 (1.3)	1–5	NS
Duration of sleep at baseline, h	3.8 (1.2)	1–5.5	3.8 (1.4)	2–6	NS
Duration of sleep at endpoint, h	5.9 (0.9)	4–7	5.0 (1.6)	2–7	t = 1.79, df = 22, p = .08
Global experience of benefit[a]	2.5 (1.0)	0–4	1.6 (1.3)	0–4	t = 2.24, df = 27, p = .03

[a]As rated on a 5-point scale, with higher ratings indicating greater benefit.

Table 4. Sleep Questionnaire Results: Effects on Sleep

Item	Days That Melatonin Was Superior to Placebo[a]
Drowsiness	...
Time to fall asleep	1, 2[b]; 3, 4; 13, 14[b]
Quality of sleep	1, 2[b]; 3, 4[b]; 5, 6; 7, 8[b]; 9, 10[b]; 11, 12[b]; 13, 14; 15, 16[b]
Depth of sleep	1, 2; 3, 4; 5, 6; 7, 8[b]; 9, 10; 13, 14[b]
No. of dreams	...
Quality of dreams	...
Time of morning awakening	...
Freshness on awakening	1, 2; 3, 4
Freshness during the day	1, 2[b]
Mood	...
Overall level of functioning	1, 2[b]

[a]Placebo was not superior to melatonin on any of the items on any of the days of the study. Data were analyzed using the Mann-Whitney U test. Symbol: … = no difference.
[b]Days on which there was a trend (.05 < p < .10) toward an advantage with melatonin. For all other days, p < .05.

found the medication ineffective. In line with previous findings,[8] benefits with melatonin were modest; sleep-onset latency improved by a mean of 1.1 hours in the melatonin group and 0.8 hours in the placebo group. Similarly, sleep duration increased by 2.1 hours in the melatonin group and 1.2 hours in the placebo group. Since melatonin is very rapidly metabolized,[11,14] an issue worth examining in future research is whether a sustained-release formulation of melatonin would yield more impressive results.[12]

On certain items in the sleep questionnaire, benefits with melatonin were significantly superior to placebo, chiefly early during the course of treatment (see Table 4). There are 3 possible explanations for this finding. One is that patients develop tolerance to the sleep-related benefits with melatonin. Another is that improvement in the primary medical condition, associated with inpatient treatment, led to improvement in sleep function in both groups, thus making it less likely that melatonin-mediated benefits would be perceptible (ceiling effect).

The third explanation is that the wording of response choices on the sleep questionnaire might have obscured true benefits with melatonin. Each item was scored along a continuum, i.e., 0 = worse than usual, 1 = same as usual, and 2 = better than usual. Following initial improvement with melatonin, better sleep functioning might have become "usual" to the patient; as a result, as days passed, the maintenance of improved sleep functioning would have received a rating of 1. In contrast, in placebo-treated patients, a rating of 1 would have been assigned to a failure to improve. Thus, the same rating would have been assigned to 2 different outcomes, leading to a lack of significant differences between groups even though a true difference may have existed. The fact that a true difference did exist is suggested by the data recorded in Table 3: at endpoint, melatonin-treated patients were falling asleep earlier and were sleeping longer than the placebo-treated patients.

In summary, in medically ill patients with initial insomnia, melatonin hastened sleep onset without producing drowsiness, improved the quality and depth of sleep, increased the duration of sleep, and increased morning freshness on awakening. The modal preferred dose of melatonin was 6 mg/night. Melatonin was very well tolerated, and its abrupt discontinuation was associated with no withdrawal symptoms.

A limitation of this study is that polysomnographic and other objective measures of sleep were not obtained. However, subjective benefits reported by patients are also important and merit attention. The results of this study must be viewed with some caution because of the heterogeneous diagnoses, the small sample sizes, the short duration of treatment, and the examination of trends toward significance. Nevertheless, the consistent patterns favoring melatonin on certain specific measures suggest grounds for optimism and further investigation of short- and long-term benefits with melatonin in medically ill patients with initial insomnia. Finally, although no adverse effects were associated with melatonin in this study, it is acknowledged that occasional reports of melatonin-related treatment-emergent events do exist; these require systematic evaluation in future research.[1,16]

Drug name: fluoxetine (Prozac).

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Appendix 1. Sleep Questionnaire Items[a]

Items related to efficacy
1. Experience of drowsiness after taking melatonin
2. Time to fall asleep
3. Quality of sleep
4. Depth of sleep
5. Quantity of dreams
6. Quality of dreams
7. Time of morning awakening
8. Freshness on awakening
9. Freshness during the day
10. Effects on mood
11. Effects on overall level of functioning

Items related to adverse effects
12. Headache
13. Heaviness in the head
14. Mental dullness
15. Duration of the longest symptom

[a]The sleep questionnaire posed each of the above items in the form of an appropriately worded question. Items 1–11 were self-assessed by the patient using a 3-point scale of the following general form: 0 = The medication had a negative effect, or functioning was poorer than usual; 1 = The medication did not appear to have any effect, or functioning was rather the same as usual; and 2 = The medication had a positive effect, or functioning was better than usual. Items 12–14 were self-assessed on a 0–3 scale that described the symptoms as absent, mild, moderate, or severe, and item 15 was rated in units of time. The wording of the response choices was individualized for the items in the questionnaire.

The full text of the questionnaire is available from the first author (C.A.).

Appendix 2. Withdrawal Symptom Checklist[a]

Headache
Muscular aches and pains
Muscular cramps
Tremors
Physical fatigue
Physical restlessness
Tingling, numbness, or other unusual sensations
Anxiety, tension, uneasiness, or inability to relax
Depression
Irritability
Mental fatigue
Poor concentration
Palpitations
Flushing, feeling warm all over
Sweating
Dryness of mouth
Blurring of vision
Dizziness or blackouts
Unsteadiness
Nausea, vomiting
Abdominal discomfort
Diarrhea
Frequent urination
Loss of appetite
Disturbed sleep

[a]Symptoms to be recorded if developing on days 1–3 after drug discontinuation.