Melatonin in Schizophrenic Outpatients With Insomnia: A Double-Blind, Placebo-Controlled Study

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Dr. Andrade has received a grant from Aristo Pharmaceuticals, Ltd., Bombay, India, to study the effects of melatonin in medically ill patients with insomnia. The present study, however, was unfunded, although Aristo Pharmaceuticals, Ltd., did supply the melatonin and placebo samples for the study. Aristo Pharmaceuticals played no role in the design or analysis of either study or in the preparation of either manuscript for publication.

Drs. Kumar, Bhakta, and Singh report no additional financial or other relationship related to the subject of this article.

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Background: Low nighttime levels of melatonin have been demonstrated in patients with insomnia, and melatonin has been shown to have hypnotic properties in some groups of such subjects. Low melatonin levels have also been observed in patients with schizophrenia; however, there is little literature on the efficacy of exogenous melatonin in treating insomnia associated with schizophrenia.

Method: Stable DSM-IV schizophrenic outpatients (N = 40) with initial insomnia of at least 2 weeks' duration were randomly assigned to augment their current medications with either flexibly dosed melatonin (3–12 mg/night; N = 20) or placebo (N = 20). By use of a questionnaire, double-blind assessments of aspects of sleep functioning were obtained daily across the next 15 days. The study was conducted between March and December 2002.

Results: The modal stable dose of melatonin was 3 mg. Relative to placebo, melatonin significantly improved the quality and depth of nighttime sleep, reduced the number of nighttime awakenings, and increased the duration of sleep without producing a morning hangover ($p < .05$). Subjectively, melatonin also significantly reduced sleep-onset latency, heightened freshness on awakening, improved mood, and improved daytime functioning ($p < .05$).

Conclusion: Melatonin may be a useful short-term hypnotic for schizophrenic patients with insomnia. Melatonin could be considered for patients in whom conventional hypnotic drug therapy or higher sedative antipsychotic drug doses may be problematic.

(J Clin Psychiatry 2007;68:237–241)

Sleep is an important restorative physiologic process. Neurotransmitters such as melatonin, acetylcholine, serotonin, norepinephrine, and others are involved in the induction and maintenance of sleep.[1,2] Disturbance of sleep or secondary insomnia is often associated with psychiatric disorders, as well as with many medical and surgical conditions.[3]

Melatonin (N-acetyl-5-methoxytryptamine), an endogenous sleep promoter, is a hormone secreted by the pineal gland. Melatonin levels peak at night; the diurnal variation is synchronized by the light-dark cycle and helps to maintain the circadian rhythm.[1] Low nighttime levels of melatonin and disturbances in the diurnal variation in melatonin secretion are associated with insomnia.[4]

Exogenous melatonin has been successfully used for the treatment of insomnia associated with disturbed patterns of melatonin secretion. Conditions in which exogenous melatonin has proved therapeutic include sleep phase disorders such as jet lag and shift work[5] as well as blindness.[6] Melatonin has also been shown to have hypnotic properties in insomnia associated with old age.[7] Mania[8] and medical illness[9] are other conditions in which melatonin has been successfully used to treat insomnia.

Schizophrenia is a psychiatric disorder characterized by delusions, hallucinations, and deterioration of functional abilities.[3] Patients with schizophrenia commonly experience insomnia; delay in sleep onset and problems with sleep maintenance have both been described.[10,11] In some affected patients, the poor sleep quality or decrease in total sleep time may impair quality of life to such an extent that it warrants independent clinical attention.[10,11]

The nighttime peak in melatonin secretion is blunted in drug-free schizophrenic subjects; there is no correction in this pattern even after the patients improve with antipsychotic drug therapy.[12,13] Patients with chronic illness have lower nighttime melatonin levels than those with early-stage illness.[14] These findings notwithstanding, there has been little study of the usefulness of melatonin in the treatment of insomnia associated with schizophrenia. The present study, therefore, sought to examine whether melatonin conveys benefits to schizophrenic patients who complain of insomnia.

METHOD

The sample comprised 40 physically healthy, adult outpatients diagnosed with DSM-IV[3] paranoid schizophrenia. All patients had been ill for less than a year, were clinically stable, and had been receiving the same dose of psychotropic medication (haloperidol, 10–15 mg nightly) for at least the past 1 month. All patients complained of initial insomnia, 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. After providing written informed consent for participation in the study, the subjects were randomly assigned to augment their current prescription with either melatonin (N = 20) or lactose placebo (N = 20), administered in the form of identical capsules. Each melatonin capsule contained 3 mg of the hormone. The medications were supplied by Aristo Pharmaceuticals Ltd., Mumbai, India. The study was conducted between March and December 2002. Institutional review board approval was obtained.

Medication dosing was patient determined and was flexible, 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 period of 15 days. Behavioral counseling to improve sleep was not provided. The psychotropic medications that the patients had been receiving were continued unchanged throughout the study.

Information obtained at baseline and endpoint included the average time it had taken to fall asleep during the previous 3 days, the average number of nighttime awakenings, and the average duration of nighttime sleep. Patients were also self-assessed at baseline, each day 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. This questionnaire was developed by one of the authors (C.A.) and had been found satisfactory in a previous randomized, double-blind, placebo-controlled study[9] of the effects of melatonin in medically ill patients with insomnia. The questionnaire was completed each afternoon and focused on the effects of the previous night's medication. Both patients and rater were blind to treatment status.

Table 1. Sample Description

Characteristic	Melatonin (N = 20)	Placebo (N = 20)	Significance		
			Statistic	df	p
Age, mean (SD), y	38.4 (14.4)	36.0 (13.4)	t = 0.55	38	.59
Sex, N			χ^2 = 0.11	1	.74
Male	13	14			
Female	7	6			

Statistical Method

To reduce the number of data points, data from the questionnaire were pooled into 5-day blocks as follows: days 1 to 5, days 6 to 10, and days 11 to 15. 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 test (with z corrected for ties) was employed. The χ^2 test was used to compare frequency distributions between groups. Repeated-measures multivariate analysis of variance was used to compare means between groups and across time. All tests of significance, wherever applicable, were 2-tailed. Alpha for significance was set at .05; the modest risk for type 1 errors was offset by the predominant use of nonparametric tests, which are known to be conservative.

RESULTS

The melatonin and placebo groups were similar in age and sex (Table 1). At baseline, the 2 groups did not differ significantly in time to fall asleep (z = 0.44, p = .66), number of nighttime awakenings (z = 1.49, p = .14), and total duration of nighttime sleep (z = 0.87, p = .38) (Table 2).

At endpoint, the melatonin-treated patients showed a significantly greater reduction in the number of nighttime awakenings (p = .045) and slept for longer than did the placebo-treated patients (p = .021); however, the numerically greater improvement in sleep-onset latency was not statistically significant (Table 2).

The results of the analysis of the sleep questionnaire data are summarized in Table 3. Relative to placebo, melatonin significantly reduced sleep latency and improved the quality and depth of sleep during the initial 10 days of treatment. Melatonin was associated with significantly better mood during the first and third 5-day blocks. Patients receiving melatonin experienced greater early-morning freshness all through the study and better overall

Table 2. Patients' Self-Report of Sleep at Baseline and Endpoint[a]

Item	Melatonin (N = 20)	Placebo (N = 20)	Significance		
			F	df	p
Time to fall asleep					
Baseline, h[b]	2.01 (1.34)	1.70 (0.72)			
Endpoint, h	1.14 (1.21)	1.11 (0.53)	0.79[c]	1,38	.38
No. of nighttime awakenings					
Baseline[b]	1.83 (1.09)	2.30 (0.73)			
Endpoint	0.75 (0.91)	1.70 (0.57)	4.30[c]	1,38	.045
Duration of sleep					
Baseline, h[b]	4.6 (1.5)	5.1 (0.9)			
Endpoint, h	5.7 (1.6)	5.4 (0.9)	5.79[c]	1,38	.021

[a]Data presented are mean (SD).
[b]The drug and placebo groups did not differ significantly at baseline.
[c]Drug × time interaction.

Table 3. Sleep Questionnaire Results: Effects on Sleep

Item	Blocks of Days During Which Melatonin Was Superior ($p < .05$) to Placebo[a]
Drowsiness after taking medication	none
Time to fall asleep	(1–5); (6–10)
Quality of sleep	(1–5); (6–10)
Depth of sleep	(1–5); (6–10)
Number of dreams	none
Quality of dreams	none
Time of morning awakening	none
Freshness on awakening	(1–5); (6–10); (11–15)
Morning headache	(6–10); (11–15)
Morning heaviness of head	none
Morning mental dullness	(1–5); (11–15)
Freshness during the day	none
Mood	(1–5); (11–15)
Overall functioning	(1–5)

[a]Placebo was not superior to melatonin on any of the items during any of the blocks of days in the study.

functioning during the first 5-day block. There were no significant differences between the 2 groups in the experience of drowsiness after taking the nighttime medication, in the number or quality of dreams recalled, in the time of awaking in the morning, in the experience of heaviness of the head on awaking in the morning, and in the experience of freshness during the day. Melatonin, however, was associated with less experience of morning headache during days 6–15, and with less mental dullness during days 1–5 and 11–15.

The average number of capsules consumed per 5-night block increased across time in the placebo group but not in the melatonin group (Table 4). The modal dose in the melatonin group was 1 capsule (3 mg) per night across the entire study period.

Table 4. Mean (SD) Number of Capsules Consumed During Each 5-Night Block[a]

Day	Melatonin (N = 20)	Placebo (N = 20)
1–5	6.15 (1.39)	6.85 (1.73)
6–10	7.25 (2.05)	8.45 (1.64)
11–15	5.80 (1.47)	8.95 (2.19)

[a]Drug × time interaction, Pillai's trace = 0.49, F = 17.76, df = 2,37; $p < .001$.

DISCUSSION

Insomnia in patients with schizophrenia can be pharmacologically treated by increasing the dose of antipsychotic medicine, by adding a sedating antipsychotic, or by prescribing a hypnotic drug. All 3 options carry disadvantages. Increasing the antipsychotic load in the prescription could increase extrapyramidal symptoms, cognitive impairment, and other adverse effects related to the use of these drugs. The use of conventional hypnotic drugs carries the risk of rebound insomnia upon withdrawal of the drug or even drug dependence.[15] Melatonin has been suggested to have hypnotic properties in diverse populations,[5–9] and meta-analyses have suggested that the drug is well tolerated and has a placebo level of adverse effects, at least in the short term.[16,17] We therefore conducted this study with a view to determine whether melatonin conveys clinically worthwhile benefits in schizophrenic patients with insomnia.

Two recent meta-analyses suggested that melatonin conveys little or no benefit to patients with primary and secondary sleep disorders[16,17]; however, there was only 1 study included in these meta-analyses that examined the usefulness of melatonin specifically in schizophrenia, a condition characterized by a disturbed pattern of melatonin secretion. Our findings in a schizophrenic sample were encouraging. We observed that, relative to placebo, melatonin significantly improved the quality and depth of nighttime sleep, reduced the number of nighttime awakenings, and increased the duration of sleep without producing drowsiness or early-morning hangover. Melatonin also reduced sleep-onset latency, heightened freshness on awaking, and improved mood. Other benefits with melatonin included decreased headache and mental dullness on awaking in the morning and improved functioning during the day. Most of these benefits were apparent on most of the days of the study. These benefits with melatonin were obtained with a modal dose of 3 mg nightly. Whereas the melatonin dose tended to remain relatively stable throughout the study period, that of placebo rose significantly, no doubt because patients found it ineffective.

Our results confirm and add to the findings of the only other team to have worked on the subject. Shamir et al.[18] conducted a 3-week, double-blind, placebo-controlled, crossover study of controlled-release melatonin (2 mg nightly) in 19 patients with chronic schizophrenia. They found that there was a small but statistically significant improvement in sleep efficiency during the melatonin phase relative to the placebo phase of the study; these

benefits were greater in patients with initially lower sleep efficiency.

In our study, melatonin was associated with a broad spectrum of sleep-related benefits without an associated burden of sedative adverse effects during the morning and day; in fact, on many parameters, such as morning freshness, morning headache, morning dullness, daytime mood, and daytime levels of functioning, melatonin was associated with better outcomes than placebo. 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.[19] The use of melatonin, therefore, appears advantageous for the treatment of insomnia in schizophrenic patients; it does not occasion neurobehavioral impairments as do drugs such as temazepam, as demonstrated in a direct comparison of this drug with melatonin.[20] From a theoretical perspective, the administration of exogenous melatonin may be useful because there is a blunting in the nighttime peaking in the levels of endogenous melatonin in patients with schizophrenia; this is evident not only in drug-free patients but also in treated patients who have responded to antipsychotic medication.[12,13,21]

The experience of insomnia can be stressful, and stress can worsen psychopathology in schizophrenic patients. The successful treatment of insomnia can reduce ratings of illness severity and improve ratings of quality of life. The results of our study therefore suggest that, in schizophrenic patients with insomnia, melatonin may convey at least short-term improvements in ratings of illness and of quality of life without need for an increase in the antipsychotic medication dose. This is a matter that may merit further study.

Limitations

Our study had several limitations. We used a parallel-group design rather than a crossover design; thus, the effects of melatonin and placebo were not examined in each patient. However, we believe that because we had randomly assigned patients to the treatment groups, the risk of bias was small. We did not obtain melatonin levels; these could have helped to determine whether the benefits with exogenous melatonin were selectively related to lower levels of endogenous hormone. We did not study sleep habits in our patients; inappropriate sleep habits (such as taking daytime naps or sleeping with bright lights on) can compromise nighttime sleep. Nonetheless, whatever the sleep habits of our patients, melatonin was clearly superior to placebo.

We did not obtain objective measures of sleep through polysomnographic or actigraphic evaluations. However, subjective benefits reported by patients are also important and merit attention. We did not formally rate psychopathology and assess the relationship thereof to the presence of insomnia and the response of this symptom to melatonin; however, because subjects for this study were preselected both for clinical stability during the previous month and for the presence of insomnia as the sole complaint requiring clinical attention, it is unlikely that psychopathology would have been an influencing factor in either regard. It is conceivable that the antipsychotic medications that a patient receives may influence the response of insomnia to melatonin; this was not a confound in our study because all patients were receiving the same drug, haloperidol, in a narrow dose range (10–15 mg nightly).

We do not know what the optimum dose of melatonin is; this would need to be identified in dose-ranging studies. A formal evaluation of the adverse effects of treatment is necessary, although existing data from meta-analyses suggest that these adverse effects are likely to be no greater than those with placebo.[16,17] Finally, the results of this study must be viewed with some caution because of the modest sample size and the short duration of treatment; whereas the sample size was sufficient to demonstrate the superiority of melatonin over placebo on various measures of sleep, we acknowledge that studies of longer duration are necessary to determine the persistence of benefits with melatonin into the intermediate or even long term.

Drug names: haloperidol (Haldol and others), temazepam (Restoril and others).

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