Melatonin Improves Sleep Quality of Patients With Chronic Schizophrenia

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Background: Accumulating evidence indicates decreased melatonin levels in patients with schizophrenia. Insomnia, mainly difficulty in falling asleep at night, is commonly reported in this population. Association of insomnia with low or abnormal melatonin rhythms has been repeatedly documented. Melatonin is an endogenous sleep promoter in humans. We hypothesized that insomnia in patients with schizophrenia may be partially due to diminished melatonin output. In this study, we measured melatonin output in patients with chronic schizophrenia and assessed the effects of melatonin replacement on their sleep quality.

Method: In a randomized, double-blind, crossover, clinically based trial, 19 patients with DSM-IV schizophrenia who were treated with the normal treatment regimen were given melatonin (2 mg, controlled release) or placebo for 2 treatment periods of 3 weeks each with 1 week washout between treatment periods (7 weeks total). For measuring endogenous melatonin production, urine was collected from each patient every 3 hours between 9:00 p.m. and 9:00 a.m. Actigraphy was performed for 3 consecutive nights at the end of each period. Activity- and rest-derived sleep parameters were compared for the whole population with treatment arm as the intervening variable. A separate analysis was performed for patients subgrouped into high versus low sleep efficiency.

Results: All patients had low melatonin output. Melatonin replacement significantly improved rest-derived sleep efficiency compared with placebo (83.5% vs. 78.2%, $p = .038$) in this population. Improvement of sleep efficiency was significantly greater ($p < .0014$) in low-efficiency (80% vs. 67%) than high-efficiency sleepers (88% vs. 90%). In addition, during melatonin therapy, tendencies toward shortened sleep latency (by 40 minutes, $p < .056$) and increased sleep duration (by 45 minutes, $p < .078$) were observed in low- but not high-efficiency sleepers.

Conclusion: Melatonin improves sleep efficiency in patients with schizophrenia whose sleep quality is low.

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Schizophrenia is a psychiatric disorder characterized by delusions, hallucinations, and a general deterioration in level of functioning.[1] Sleep disturbances are commonly reported in patients with schizophrenia,[2] often presenting disturbances of sleep initiation and continuity, especially in acute phases of the illness.[3] Prolonged sleep-onset latency, increased wake after sleep onset duration, and decreased stage 2 sleep were demonstrated in polysomnographic studies of patients with schizophrenia.[4] The severity of sleep disturbances in patients with schizophrenia parallels the intensity of their clinical symptoms: significant correlation has been demonstrated between sleep latency and the thinking disturbances factor assessed by the Brief Psychiatric Rating Scale (BPRS).[5]

Melatonin (*N*-acetyl-5-methoxytryptamine) is produced at night by the pineal gland and secreted into the plasma in a circadian rhythm, which is synchronized by the light-dark cycle.[6,7] Melatonin plays a major physiologic role in the regulation of sleep,[8] and a large body of evidence indicates decreased melatonin levels in patients with schizophrenia.[9–13] In addition, alterations in both the circadian rhythm of melatonin and the rest-activity cycle have been demonstrated in patients with schizophrenia.[14,15]

Association of insomnia with low or distorted melatonin rhythms has been documented in a number of studies. Nocturnal plasma melatonin levels in young and middle-aged patients experiencing primary insomnia were significantly lower than those of healthy controls.[16–26] We have previously shown that urinary excretion of 6-sulfatoxymelatonin (6-SMT) was significantly lower and its peak delayed in healthy elderly insomniacs, but not in age-matched controls who did not complain of insomnia.[16] Furthermore, elders who complained about insomnia or depression were found to frequently present

disturbed 6-SMT excretion rhythms, and those with more deviant acrophases displayed more disturbed sleep.[20] In age-related sleep-maintenance insomnia, 50% of the patients had low melatonin output.[21] In addition, total sleep time and sleep efficiency in these patients correlated with the timing of the offset of the endogenous melatonin rhythm.[21] Another study[22] failed to show correlation between measure and amplitude of 6-SMT rhythms and sleep in a mixed population of volunteers (60–79 years of age) who complained of insomnia or depression. Nevertheless, significant correlations were found in that group between mean 6-SMT levels during the sleep period and total sleep time and wake after sleep onset.[22] Sleep abnormalities in chronic heart patients and hypertensive patients treated with β-blockers have been shown to be accompanied by impairment in the nocturnal release of endogenous melatonin.[23,24] Clonidine and nonsteroidal anti-inflammatory drugs occasionally cause insomnia, consistent with their effects on melatonin.[25] A recent study demonstrated a significant association between a higher pineal calcification and the presence of sleep disturbances and daytime tiredness in humans.[26] A correlation between pineal calcification and reduced melatonin production was also noted.[27] We have therefore hypothesized that sleep disorders in patients with schizophrenia are at least partially due to diminished melatonin output. Accumulating data demonstrate beneficial effects of melatonin in sleep induction and maintenance in insomnia, particularly in elderly patients and in patients with decreased melatonin output.[28–33] The main objectives of this investigation were to measure 6-SMT excretion in patients with chronic schizophrenia and assess the effects of melatonin treatment on the quality of their sleep. To our knowledge, this is the first report examining the effect of melatonin on patients with schizophrenia.

METHOD

Twenty-seven outpatients diagnosed with schizophrenia (according to DSM-IV criteria)[1] and who complained of poor sleep quality and were diagnosed for insomnia (according to DSM-IV) were included in the study. Patients with liver or renal diseases (serum creatinine level above 1.5 mg/dL) or with other psychiatric or severe physical diseases were excluded. Despite having schizophrenia, 23 of 27 patients cooperated and complied with all the phases of the trial; 4 patients dropped out owing to lack of compliance with the study protocol. Of these, only 1 patient with schizophrenia of the paranoid type could not tolerate the actigraph.

Efficacy data of another 4 patients were missing because of technical problems with the operation of the actigraphs. The data of the 19 patients for whom efficacy data were available are reported. All patients were interviewed by 2 board-certified psychiatrists, and diagnosis was made according to DSM-IV criteria for schizophrenia. Of these patients (12 men and 7 women; mean ± SD age = 42 ± 5 years; range, 24–67 years), 9 had paranoid schizophrenia, 5 had disorganized schizophrenia, and 5 had schizoaffective disorder. All patients were taking between 1 and 3 different drugs for their primary disorder as follows: neuroleptics, 19/19; benzodiazepines, 9/19; selective serotonin reuptake inhibitor antidepressants, 3/19; and other drugs, 5/19.

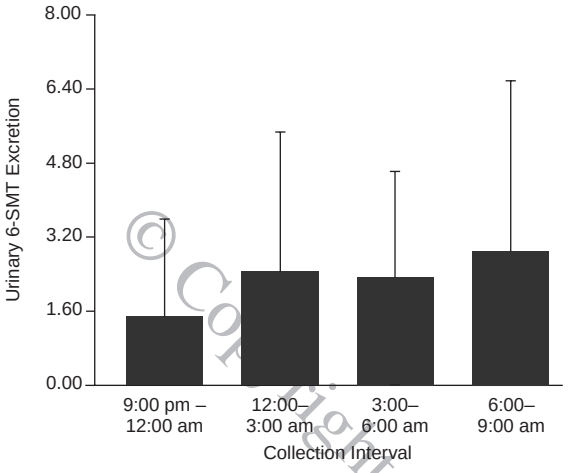
The study was designed as a crossover trial, so that the effects of placebo as well as melatonin were assessed in each patient to minimize variability arising from the differences in concomitant therapies. Concomitant drug therapy was not changed during the trial.

The clinical study was performed in accordance with the guidelines set by the World Medical Assembly, i.e., the latest version of the Declaration of Helsinki. All participants were presented with full details of the study in both verbal and written form by the investigator. Informed consent was obtained before participation in the study from each subject after the procedures and possible side effects were fully explained.

Before entering the study, subjects were awakened at 3-hour intervals overnight (9:00 p.m.–9:00 a.m.), urine was collected, volume was measured, and urine samples (1 mL) from each collection period were then frozen until assayed. Urinary 6-SMT was assayed in duplicate by radioimmunoassay (Stockgrand Ltd., Surrey, England).

In a randomized, double-blind, crossover manner, subjects were given either 2 mg of melatonin in a controlled-release formulation (Circadin; Neurim Pharmaceuticals, Tel Aviv, Israel) or a placebo identical in appearance. The tablets were taken once daily 2 hours before the desired bedtime for a period of 3 weeks, with 1-week placebo washout period between 2 treatment periods. During the last week of each treatment period, the quality of sleep was objectively assessed for 3 consecutive nights by wrist actigraphy (Somnitor; Neurim Pharmaceuticals, Tel Aviv, Israel) at each subject's home. The whole crossover study duration was 7 weeks. Actigraphic motion recordings were averaged over the 3 night recording periods in each patient and analyzed using an automatic scoring algorithm to determine activity- and rest-derived sleep/wake episodes. The main objective was to compare the effect of melatonin versus placebo on sleep efficiency (percentage of total time asleep over total time in bed). In addition, the following sleep parameters were compared: sleep latency (time between bedtime and sleep onset), total sleep time (time spent asleep after sleep onset), wake after sleep onset duration (mid-sleep arousal time after sleep onset), fragmentation index (percentage of number of quiet episodes that are shorter than 1 minute over the total number of quiet episodes during time in bed), and the number of awakenings (the total number of awakenings during sleep).

Figure 1. Nightly 6-Sulfatoxymelatonin (6-SMT) Excretion in Urine Collected Every 3 Hours Over a 12-Hour Period[a]



[a]Data are shown as μg of 6-SMT excreted per 3-hour interval (mean ± SD).

Patients' sleep data were analyzed by means of 6 t tests for paired samples (1 for every parameter); comparisons were made between placebo and melatonin treatments.

RESULTS

The mean ± SD urinary excretion of 6-SMT by the study population is shown in Figure 1. The mean amount of 6-SMT excreted per hour did not significantly differ between collection intervals across the night. The mean total amount of 6-SMT excreted per the nocturnal 12-hour collection period was 9.6 ± 6.4 μg. This amount is lower than that reported to be excreted at night by healthy young or elderly subjects with good sleep quality.[16]

The results of the trial indicated that sleep efficiency significantly improved during melatonin treatment compared with placebo (83.5% ± 10.3% vs. 78.2% ± 14.6%; t = 2.23, df = 18, p = .038). The mean ± SD values of the various sleep parameters of the patients at the end of the placebo and melatonin treatment periods were not significantly different (Table 1). We also evaluated whether the improvement of sleep was more pronounced in the patients with more disturbed sleep. This was accomplished by reanalyzing the data separately for half of the study population whose sleep efficiency while taking placebo was lower than the median (81%) and the other half whose sleep efficiency on placebo was higher than the median value.

The patient groups displaying high and low efficiency while taking placebo had comparable low 6-SMT excretion (mean ± SD = 5.8 ± 6.1 vs. 8.0 ± 6.6 μg/night, respectively) and did not differ significantly in number of benzodiazepine users (6 vs. 3 patients, respectively).

Repeated-measurements analyses of variance (ANOVAs) were performed with the between-subjects factor (lower- vs. higher-than-median sleep efficiency), comparing the placebo and melatonin periods. Significant interactions of effect and group were obtained for sleep efficiency. Sleep efficiency was markedly (13% increase on average) and significantly (p < .0014) improved with melatonin compared with placebo (80% vs. 67%, respectively) in the subjects whose sleep efficiency with placebo was lower than the median (Figure 2). In this group, sleep latency tended to decrease and total sleep time tended to increase with melatonin compared with the respective values with placebo (68 vs. 26 minutes and 410 vs. 445 minutes, respectively) without reaching significance (p = .056 and p = .078, respectively).

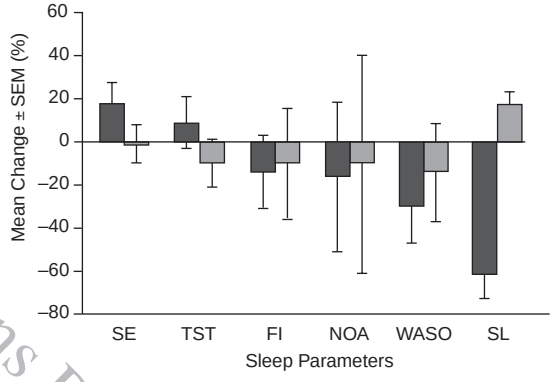
On the other hand, in the patients whose sleep efficiency with placebo was higher than the median, mean sleep efficiency did not further improve with melatonin compared with placebo (88% vs. 90%, respectively). Mean sleep latency and total sleep time did not improve and actually slightly deteriorated without reaching significance (23 vs. 27 minutes and 533 vs. 480 minutes, respectively).

Table 1. Sleep Parameters Determined by Actigraphy at the End of Melatonin- and Placebo-Treatment Periods in Patients With Schizophrenia[a]

Parameter	Placebo	Melatonin	p Value
Sleep latency, min	46.5 ± 56.0	26.0 ± 25.4	.11
Wake after sleep onset, min	64.6 ± 46.5	47.8 ± 46.0	.13
Total sleep time, min	468 ± 138	462 ± 103	.82
Number of awakenings	16.2 ± 7.9	14.0 ± 9.7	.32
Fragmentation index[b]	30.5 ± 6.6	26.8 ± 9.4	.15

[a]All values expressed as mean ± SD of 3 nights of recordings per patient for all patients.
[b]Percentage of the number of quiet episodes < 1 min over the total number of quiet episodes during time in bed.

Figure 2. Sleep Parameters in Patients With Schizophrenia Whose Sleep Efficiency With Placebo Was Higher or Lower Than the Median (81%) (as obtained from actigraph recordings of 3-night average for each patient)[a]



[a]Abbreviations: FI = fragmentation index, NOA = number of awakenings, SE = sleep efficiency, SL = sleep latency, TST = total sleep time, WASO = wake after sleep onset. Data (mean ± SEM) are shown as percentage of difference between melatonin and placebo in patients with lower-than-median sleep efficiency (black bars) and higher-than-median sleep efficiency (gray bars).

Table 2. Sleep Parameters Determined by Actigraphy at the End of Melatonin- and Placebo-Treatment Periods in 3 Types of Schizophrenia[a]

	Disorganized		Paranoid		Schizoaffective	
Parameter	Placebo	Melatonin	Placebo	Melatonin	Placebo	Melatonin
Sleep efficiency[b]	81.2 ± 12.3	87.4 ± 6.1	78.6 ± 14.2	82.2 ± 11.7	74.6 ± 19.3	81.8 ± 11.9
Sleep latency, min	32.8 ± 23.4	22.2 ± 13.6	60.2 ± 78.4	30.9 ± 34.4	35.6 ± 21.0	21.2 ± 15.8
Wake after sleep onset, min	60.0 ± 60.5	24.8 ± 15.4	66.1 ± 36.4	60.9 ± 54.6	66.4 ± 58.1	47.0 ± 47.9
Total sleep time, min	484 ± 168	445 ± 106	492 ± 108	501 ± 105	411 ± 167	411 ± 82
Number of awakenings	13.6 ± 13.2	8.6 ± 3.3	19.2 ± 3.4	17.0 ± 9.4	13.4 ± 6.7	13.8 ± 13.3
Fragmentation index[c]	31.0 ± 2.7	21.6 ± 11.4	30.9 ± 8.7	29.6 ± 8.5	29.4 ± 5.9	27.0 ± 8.7

[a]All values expressed as mean ± SD of 3 nights of recordings per patient for all patients.
[b]Percentage of total time asleep over total time in bed.
[c]Percentage of the number of quiet episodes < 1 min over the total number of quiet episodes during time in bed.

To check whether the 3 subtypes of schizophrenia differed in response to melatonin treatment, the effects of melatonin on sleep were analyzed separately for the 3 subtypes (Table 2). Repeated-measurements ANOVAs were performed separately for each of the sleep parameters in which the repeated measures were the readings under placebo and melatonin and the between-subject factor was schizophrenia subtype. No main effect of group was obtained for any of the sleep parameters. Additional analysis using the Wilcoxon matched-pair and signed-rank tests led to similar results (data not shown). We found no significant relationship between concomitant therapy and the sleep efficiency with placebo or the improvement of sleep quality with melatonin treatment.

DISCUSSION

The results of the present study demonstrate for the first time a clear beneficial effect of melatonin on improving sleep efficiency in patients with schizophrenia. The improvement in sleep efficiency was significant, whereas the 2 factors that determine this value (sleep latency and wake after sleep onset duration) decreased without being significant. This suggests that improvement in sleep initiation and/or maintenance contributed to the overall improvement in sleep efficiency. The results also indicate that patients with more disturbed sleep benefit from melatonin therapy, whereas those who have milder disturbances do not. This finding could be explained by a ceiling effect, that is, that sleep could not be improved beyond a certain quality. Another possibility is that some of the patients improved with placebo alone and were thus less responsive to the active drug. Interestingly, in those patients showing more disturbed sleep with placebo, the increase in sleep efficiency was mostly due to shortening of sleep latency; hence, total sleep time increased. Improvement of sleep latency by melatonin therapy in insomniacs has been reported in a number of recent studies,[28–33] whereas improvement in sleep efficiency has been demonstrated only in some studies in elderly insomniacs.[21,31,32] Improvement of total sleep time has been noted only in one study in elderly insomniacs,[34] but not in others, and in elderly insomniacs who were concomitantly taking benzodiazepines.[33]

The results obtained here confirm previous reports on low melatonin levels and excretion in patients with schizophrenia.[9–13] The mean excretion of 6-SMT (namely, 9.6 μg/night) is much lower than the expected output of the pineal gland in healthy young adults (35–50 μg melatonin, which would be equivalent to 50–70 μg of 6-SMT per night). Since melatonin is involved in the regulation of sleep,[8,35] it is possible that melatonin deficiency represents a major cause for insomnia in these patients. It should be noted that the low 6-SMT output was observed in all the study population, including those showing higher-than-median sleep efficiency values. This may mean that the relationship between melatonin output and sleep quality is not linear or that the 2 measures are not intrinsically coupled. The lack of direct correlation may also be due to the great intersubject variability in melatonin levels in the general population.[36]

We found no significant variance in response to melatonin among the 3 subtypes of schizophrenia. This does not necessarily indicate that melatonin has beneficial effects on sleep quality in all types of schizophrenia. Notably, the paranoid patients with schizophrenia tended to be less responsive to melatonin treatment (compared with placebo) than the other 2 groups. It remains for further studies with more patients of each subtype to determine if there are disorder-dependent differences in the response to melatonin in schizophrenia.

Drug name: clonidine (Catapres and others).

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