A Randomized, Double-Blind, Placebo-Controlled Crossover Study of the Effect of Exogenous Melatonin on Delayed Sleep Phase Syndrome

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Objective: The effects of exogenous melatonin on sleep, daytime sleepiness, fatigue, and alertness were investigated in 22 patients with delayed sleep phase syndrome whose nocturnal sleep was restricted to the interval from 24:00 to 08:00 hours. This study was a randomized, double-blind, placebo-controlled crossover trial. Subjects received either placebo or melatonin (5 mg) daily for 4 weeks, underwent a 1-week washout period, and then were given the other treatment for an additional 4 weeks. Patients could take the melatonin between 19:00 and 21:00 hours, which allowed them to select the time they felt to be most beneficial for the phase-setting effects of the medication. **Methods:** Two consecutive overnight polysomnographic recordings were performed on three occasions: at baseline (before treatment), after 4 weeks of melatonin treatment, and after 4 weeks of placebo treatment. **Results:** In the 20 patients who completed the study, sleep onset latency was significantly reduced while subjects were taking melatonin as compared with both placebo and baseline. There was no evidence that melatonin altered total sleep time (as compared with baseline total sleep time), but there was a significant decrease in total sleep time while patients were taking placebo. Melatonin did not result in altered scores on subjective measures of sleepiness, fatigue, and alertness, which were administered at different times of the day. After an imposed conventional sleep period (from 24:00 to 08:00), subjects taking melatonin reported being less sleepy and fatigued than they did while taking placebo. **Conclusions:** Melatonin ameliorated some symptoms of delayed sleep phase syndrome, as confirmed by both objective and subjective measures. No adverse effects of melatonin were noted during the 4-week treatment period. **Key words:** melatonin, delayed sleep phase syndrome, sleep, circadian rhythms.

aMT6s = sulfatoxymelatonin; CES-D = Center for Epidemiologic Studies Depression Scale; DSPS = delayed sleep phase syndrome; HAM-D = Hamilton Depression Scale; REM = rapid eye movement; SOL = sleep onset latency; SSS = Stanford Sleepiness Scale; TST = total sleep time; WASO = wakefulness after sleep onset.

INTRODUCTION

DSPS, a circadian rhythm disorder, is a chronic condition characterized by the persistent inability to fall asleep and arise at conventional times (1). In patients with DSPS, sleep onset is often delayed until early morning (02:00–06:00 hours), and when no attempt is made to conform to the environment, their usual rise time may be early afternoon. Sleep architecture and the maintenance of sleep are not usually disrupted in DSPS (2); however, when patients attempt to advance their bedtime, sleep onset insomnia is experienced. It is also difficult, or impossible, for them to have a "normal" or "typical" rise time. If this regimen is enforced on a long-term basis, daytime sleepiness ensues. Onset of DSPS can occur at any age, but initial onset most commonly occurs during adolescence (3).

Weitzman et al. (1) reported that 7% to 10% of adults attending sleep disorders clinics had DSPS. A survey of students aged 12 to 20 years found that 16% had chronic difficulty falling asleep and arising in the morning and that 7.3% met the diagnostic criteria for DSPS (4). According to Regestein and Monk (2), within the clinical sleep disorder population DSPS is the most common sleep/wake scheduling disorder observed and accounts for approximately 10% of cases of chronic insomnia.

DSPS is a manifestation of a problem with the physiological timing system of the body clock. The endogenous clock time is controlled by an oscillator located within the hypothalamic suprachiasmatic nucleus. The sleep/wake system depends on the endogenous circadian rhythm of a number of biological parameters, including temperature, hormones, and metabolic parameters. The temporal cue that normally constrains the length of the endogenous circadian period to 24 hours is the ambient light/dark cycle. In some individuals this control system seems to be insufficient. For example, in the blind, those who spend the winter at higher latitudes, and those who have abnormal circadian responses to light stimuli (5–7), the endogenous period may be insufficiently synchronized to a regular 24-hour cycle using body temperature as a marker of the circadian period.

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DSPS is a debilitating condition. It is invariably associated with educational, occupational, financial, social, and marital problems, which may in turn lead to psychiatric problems (1, 2). There seems to be a strong association between DSPS and depression; Regestein and Monk (2) reported that 75% of patients with DSPS seen in a sleep clinic had current symptoms or a history of severe depression, compared with 16% of patients with chronic insomnia but not DSPS and 2% of patients with sleep apnea. The direction of causality between DSPS and depression is unclear. The sleep disturbance in DSPS differs from the sleep disturbance that often accompanies psychiatric disorders, in which it is common to find that once the psychiatric condition is treated the sleep problem diminishes. In DSPS the sleep disruption persists despite treatment for depression. This poor treatment response suggests that DSPS is a cause rather than a consequence of depression.

Despite increased awareness of the prevalence and impact of DSPS, little has been achieved in the way of treatment. Regestein and Monk (2) described the relatively unsuccessful responses to a variety of treatments, including sleep hygiene, chronotherapy, triazolam, and vitamin B_{12}. Chronotherapy is a behavioral technique in which the bedtime is systematically delayed by 3-hour increments each day until the desired bedtime is reached (3, 8, 9). This approach is highly dependent on patient compliance and motivation, resulting in a fairly low success rate; it is not used very much because patients often relapse. Another technique that has been tried in patients with DSPS is bright-light therapy, which has been shown to successfully realign the circadian phase of shift workers (10). Exposure to bright light in the morning and avoidance of light in the evening would be expected to advance sleep onset, but a significant proportion of DSPS patients are not able to wake up before noon and sometimes awaken even later.

Pharmacological approaches to the treatment of DSPS have the potential of being controlled more readily and of increasing patient compliance. One agent of interest is melatonin, which is produced by the pineal gland with a nocturnal peak of secretion during the dark period (11–17). Melatonin has been reported to have phase-shifting effects on the sleep/wake cycle (18).

The findings to date regarding melatonin treatment of DSPS are promising but limited. Deacon et al. (19) found that administration of 5 mg of melatonin immediately suppressed core body temperature and increased sleep propensity, suggesting that temperature suppression may play an integral role in phase shifting. Melatonin has been reported to advance sleep onset in patients with DSPS by 82 to 115 minutes (20–22). These studies did not include full polysomnographic measures of sleep and involved small numbers of patients. More recently Nagtegaal et al. (23) administered melatonin 5 hours before the individual's "dim-light melatonin onset." Apparently melatonin production is not influenced by sleep and activity and is masked only by bright light. Measuring the onset of melatonin secretion, which is clearly a demarcated event, can be a reliable marker for the circadian phase position. The dim-light melatonin onset has been shown to advance with exposure to bright light in the morning and to delay with exposure to bright light in the evening. A phase-response curve to melatonin in humans is a converse of the phase-response curve to light and is about 12 hours out of phase with the phase-response curve to light (24). In Nagtegaal et al.'s study, administration of exogenous melatonin (5 mg) in the evening for 4 weeks caused a predictable (in accordance with the phase-response curve) advance in the onset of the nocturnal melatonin profile of approximately 1.5 hours.

Thus, melatonin seems to be an effective treatment for DSPS. However, prospective studies of large populations of DSPS patients have not been conducted, so treatment remains empirical and intuitive.

The purpose of this study was to investigate the effect of exogenous melatonin on DSPS in a randomized, double-blind, placebo-controlled, crossover trial. A partially fixed time of melatonin administration (from 19:00 to 21:00 hours) was used, allowing patients to adjust themselves to the most beneficial phase-setting effects of the medication. We formulated the following hypotheses: 1) Administration of 5 mg of melatonin at a partially fixed time (early to mid evening) will significantly reduce SOL in DSPS patients during an imposed sleep period time (socially desirable time from 24:00 to 8:00 hours); and 2) Sleep continuity and sleep architecture will be not significantly affected by melatonin.

METHODS

Twenty-two patients (15 men aged 35.6 ± 14.0 years and 7 women aged 30.8 ± 12.4 years) with an established diagnosis of DSPS according to standard criteria of the International Classification of Sleep Disorders (25) were enrolled. Two men dropped out of the study before it was completed (one patient, after undergoing the two-night baseline polysomnographic recording, refused to spend the remaining four nights in the sleep clinic; the other one moved). Participants were recruited through a variety of sources, including advertisements placed on hospital bulletin boards, local physicians, and advertisements on television and in newspapers. The diagnostic criteria of DSPS included a primary complaint of inability to fall asleep and to wake spontaneously at the socially desirable time; phase delay of the major sleep episode in relation to the desired time

for sleep; symptoms present for at least 12 months; and absence of medical, psychological or psychiatric factors to explain the symptoms. The diagnosis was made on the basis of both the International Classification of Sleep Disorders and a clinical interview conducted by a psychiatrist-sleep specialist. Forty-seven patients were evaluated, and 22 met inclusion criteria. All subjects completed a sleep log for 2 weeks before the study, and this log was used to confirm the clinical diagnosis. At baseline (before treatment), patients were interviewed using the HAM-D (17 items) (26) and the CES-D (27). The whole sample of subjects had elevated depressive indices (mean CES-D score = 23.5 ± 6.4, mean HAM-D score = 9.4 ± 3.0).

The following exclusion criteria were applied: shift work, presence of other sleep disorders, age <16 years, alcohol or drug abuse, current use of psychotropic medications, active behavioral treatment, and severe psychiatric and neurological disorders. The study protocol was approved by the Human Ethics Committee of the Toronto Hospital, and written informed consent was obtained from all participants after the procedures had been fully explained. All subjects were asked to sign the consent form, confirming that they understood the goals, risks, and potential benefits of the study and their right to withdraw from the study at any time.

The trial was conducted over 9 consecutive weeks during one season (for each patient) to control for seasonal variations in endogenous melatonin levels. Figure 1 illustrates the design of the study. Two consecutive overnight polysomnographic studies were performed at baseline (before treatment) and at the end of 4 weeks of treatment with melatonin and after 4 weeks of treatment with placebo. Polysomnographic results obtained on the first night on each occasion were not included in the analysis to avoid a possible "first-night" effect (28). For the baseline recordings, patients chose their own retiring and wake up times as consistent with their normal routine. After the second baseline night, patients were randomly assigned to either the placebo or melatonin group. Each subject then received either 5 mg/d of melatonin or placebo (of identical appearance) for 4 weeks. The order of treatment was randomized, and no effects of order were noticed (the order of treatment was accounted for as a blocking factor). Both melatonin and placebo capsules were supplied by Penn Pharmaceutical Limited (Edinborough, UK). The medication (melatonin or placebo) was taken at 19:00 hours during the first week, between 19:00 and 21:00 hours during the second and third weeks (according to the patient's preference), and at a consistent time chosen by the patient during the fourth week. The mean time chosen by patients taking melatonin was 21:03 ± 5.7 (the second value represents standard deviation in minutes); the mean time chosen by those taking placebo was 20:57 ± 9.2 ($p > .05$). At the end of each 4-week treatment phase, two consecutive overnight polysomnographic recordings were made during the imposed sleep period (24:00 to 08:00 hours). There was a washout period of 1 week between the two treatment phases.

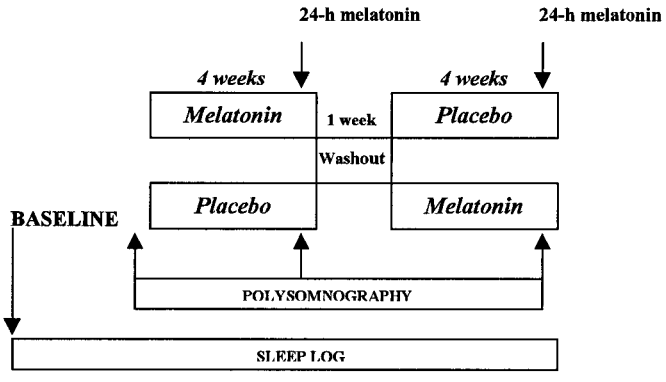

Fig. 1. Study design.

A standard polysomnographic montage was used and included electroencephalography, electrooculography, electromyography (at the chin and left and right tibialis muscles), and respiratory monitoring (oxygen saturation, nasal airflow, and breathing efforts). The polysomnograms were scored according to standardized criteria (29) by a single blinded scorer. Sleep analysis included SOL, defined as the first 30-second epoch of stage 2 sleep, slow-wave sleep, or REM sleep that was followed by no more than 1 minute of wakefulness during the first 10 minutes of sleep; TST; REM sleep latency; sleep efficiency; WASO; percentage of stage 1, 2, 3, and 4 sleep and REM sleep; number of REM episodes; arousal and periodic leg movement indexes; and respiratory disturbance index. SOL was a primary outcome measure.

Urine samples for sulfatoxymelatonin (aMT6s) measurements were collected on the 27th day of both placebo and melatonin treatment during the 24-hour period at four times: from 21:00 to 24:00 hours, from 24:00 to 08:00 hours, from 08:00 to 15:00 hours, and from 15:00 to 21:00 hours. Urine was collected under dim-light conditions during the dark period. Urine was not collected at baseline because the patients were allowed to follow their habitual routine (eg, watch TV, read, or work at late hours) and light exposure was not controlled. Immunoassays to determine the concentration of aMT6s in urine were performed according to the methods described by Aldhous and Arendt (30) using a commercial kit (CIDtech Research Inc., Mississaug, Ontario, Canada).

Before retiring to bed on the second night of each phase of the trial, patients completed the Toronto Alexithymia Scale (31, 32), a standard presleep questionnaire; the SSS (33); a seven-item Fatigue Scale; and a newly developed seven-item alertness scale, ZOGIM-A (34). On the following morning, immediately after awakening, each patient completed a standard postsleep questionnaire, the SSS, and the Fatigue Scale. Approximately 20 minutes after awakening, patients assessed their level of fatigue and sleepiness using the following scales: the Fatigue Severity Scale, the Epworth Sleepiness Scale (35), the Toronto Western Hospital Fatigue Questionnaire, the Fatigue Scale, and the FaST Adjective Checklist. The total results were reported as a composite fatigue score, which has been validated in studies on patients with multiple sclerosis (36).

After completing fatigue questionnaires, patients were asked to complete a complex verbal reasoning task (37, 38). Accuracy and time required to complete the test were assessed. To evaluate subjective circadian profiles of sleepiness, fatigue, and alertness, the patients were asked to complete the SSS, the Fatigue Scale, and the seven-item alertness scale at 2-hour intervals throughout the day starting approximately half an hour after the final awakening. This protocol was used as a substitute of the standard Multiple Sleep Latency Test (39) and Maintenance of Wakefulness Test (40) after each overnight polysomnographic study.

One-way analysis of variance was used to determine the statistical significance of sleep variables and subjective scores for the three nights from each phase of the trial. Statistically significant results detected by analysis of variance ($p < .05$) were further analyzed by using Tukey post hoc paired comparisons using the Statistical Package for the Social Sciences software (SPSS for Windows). Results in the text are expressed as mean ± standard deviation.

RESULTS

Sleep log data, recorded by the patients at home during the 2-week period before baseline laboratory parameters were measured, showed a mean lights-out

time of 2.35 ± 1.41 (number of hours and minutes, not time). Subjective SOL was 51.5 ± 53.8 minutes. The mean subjective sleep offset time was at 9.30 ± 2.05.

Objective and subjective parameters obtained in the sleep clinic in all phases of the trial are shown separately for convenience. The results of the objective measures, namely the polysomnographic sleep variables, have been separated into three categories: sleep continuity, sleep architecture, and REM sleep. Differences in sleep data at baseline, while taking placebo, and while taking melatonin are shown in Table 1.

Mean lights-out time at baseline was at 01:25 hours (range, 01:00–06:00 hours). Mean sleep offset time at baseline was at 10:40 hours (range, 09:30–13:15 hours). There was evidence of an effect of melatonin treatment on SOL. Specifically, the mean SOL for patients being treated with melatonin was significantly lower than the mean SOL for patients given placebo. Furthermore, means for both patients given melatonin and those given placebo were significantly different from the baseline mean (see Table 1). Although melatonin treatment did not significantly alter TST compared with baseline values, there was a significant decrease in TST with placebo treatment. There were no significant differences among the three groups on the other sleep continuity variables (sleep efficiency, WASO, and arousal index). Sleep architecture and REM sleep parameters were also similar for all three groups.

Results of the subjective assessments of sleepiness, fatigue, and alertness are presented in Table 2.

Scores on the SSS administered the morning after the second night of sleep revealed significant differences in subjective assessments of sleepiness during each phase of the study, with the highest sleepiness occurring while taking placebo. The mean SSS score after sleep for patients taking melatonin was significantly lower than the mean SSS score for patients given placebo (see Table 2). There were no significant differences in subjective sleepiness between groups when the SSS was administered before sleep. Fatigue Scale scores before and after sleep did not differ significantly in all three conditions. However, the composite fatigue score of patients taking melatonin was significantly lower than that of patients taking placebo. The composite fatigue score for those given placebo was significantly higher than the score obtained at baseline. The ZOGIM-A scale, which measures subjective alertness and was administered immediately after final awakening, did not reveal significant differences between the phases of the study. There were no significant differences in the circadian profiles of sleepiness, fatigue, and alertness.

There was also no significant difference in performance on the verbal reasoning task at baseline or with melatonin or placebo treatment.

We examined the association between excretion of aMT6s and objective and subjective measurements of sleep in patients with DSPS. During placebo treatment, absolute values of aMT6s excreted in urine were low, but the pattern of secretion was normal.

The repeated-measures procedure revealed a robust circadian pattern of aMT6s excretion ($F = 15.3$; $p = .0001$) in 15 of the 20 patients. There was a significant increase of nocturnal aMT6s excretion in the urine collected between 24:00 and 08:00 hours while taking placebo (Figure 2) compared with excretion of the melatonin metabolite between 21:00 and 24:00 hours (2.9 ± 6.3 vs. 24.8 ± 38.3 nmol, $p = .02$). A significant decrease of aMT6s excretion during the day from 08:00 to 15:00 hours toward evening hours from 15:00 to 21:00 hours was observed (8.5 ± 8.6 and 3.0 ± 3.5 nmol; $p = .05$ and $p = .006$, respectively). Five of the 20 patients showed an abnormal circadian pattern of melatonin secretion while receiving placebo treatment (Figure 3). Their peak excretion of aMT6s did not occur at night, as would normally be expected, but between 08:00 and 15:00 hours. These five patients had the most severe symptoms of DSPS. In three of these five patients, exogenous melatonin treatment normalized the pattern of excretion with the nocturnal peak and daytime decrease in the level of excreted aMT6s.

Oral administration of melatonin (5 mg) from 20:00 to 21:00 hours caused a rapid, approximately 100-fold increase in aMT6s excretion in urine collected between 21:00 and midnight. This high level persisted during the nocturnal hours (2379.2 ± 3860.6 vs. 1482 ± 2636.9 nmol, $p > .05$) (Figure 4).

There was an acute, significant decline of aMT6s during the daytime hours (99.0 ± 14.6 nmol, $p = .006$) and a relative increase toward the evening hours when patients were taking exogenous melatonin (733.7 ± 2143.9 nmol, $p > .05$). No gender difference in melatonin excretion was found during any phase of the trial.

DISCUSSION

Our initial hypotheses were confirmed by the results of the present investigation. In 20 patients with DSPS, administration of 5 mg of melatonin 3 to 4 hours before an imposed sleep period from 24:00 to 08:00 hours significantly decreased SOL as compared with placebo. Melatonin did not alter the other sleep parameters measured. These findings are in accordance with those of earlier open trials using smaller numbers of subjects (20, 41) and a recent double-blind placebo-

TABLE 1. Sleep Polysomnographic Variables During a 9-Week Randomized, Double-Blind, Placebo-Controlled Crossover Study of Patients With DSPS: Results at Baseline and After 4 Weeks of Melatonin or Placebo Treatment ($N = 20$)

Sleep Variable	Mean	SD	p (vs. baseline[a])	p (vs. placebo[a])	F[b]	p[b]
Sleep continuity						
SOL						
Melatonin	20.2	17.7	<.05	<.05	7.21	.005
Placebo	58.9	30.3	<.05			
Baseline	35.8	46.3				
TST						
Melatonin	404.3	60.4	>.05	<.05	5.64	.01
Placebo	382.0	55.5	<.05			
Baseline	446.1	91.6				
Sleep efficiency						
Melatonin	0.905	0.1	>.05	>.05	0.52	NS
Placebo	0.903	0.08	>.05			
Baseline	0.903	0.06				
WASO						
Melatonin	42.0	50.6	>.05	>.05	0.001	NS
Placebo	42.0	38.8	>.05			
Baseline	42.4	32.4				
Arousal index						
Melatonin	9.0	4.1	>.05	>.05	0.08	NS
Placebo	9.3	3.5	>.05			
Baseline	9.0	5.6				
Sleep architecture (%)						
Stage 1						
Melatonin	3.4	2.5	>.05	>.05	0.43	NS
Placebo	2.9	1.9	>.05			
Baseline	3.2	2.1				
Stage 2						
Melatonin	51.2	9.0	>.05	>.05	0.28	NS
Placebo	52.6	6.9	>.05			
Baseline	51.5	7.5				
Stage 3						
Melatonin	6.6	2.5	>.05	>.05	0.42	NS
Placebo	6.2	2.6	>.05			
Baseline	6.1	2.9				
Stage 4						
Melatonin	10.2	8.1	>.05	>.05	0.26	NS
Placebo	9.3	7.3	>.05			
Baseline	9.3	6.2				
REM						
Melatonin	18.3	6.9	>.05	>.05	2.12	NS
Placebo	18.6	4.3	>.05			
Baseline	20.3	5.1				
REM sleep						
REM latency						
Melatonin	72.4	21.7	>.05	>.05	1.0	NS
Placebo	71.7	26.6	>.05			
Baseline	83.4	38.9				
REM episodes[a]						
Melatonin	3.7	1.2	>.05	>.05	0.95	NS
Placebo	3.6	0.9	>.05			
Baseline	4.0	1.5				

[a] p values for Tukey post hoc analysis.
[b] Overall test for differences.

controlled study (23). The focus of our analysis was a comparison of objective polysomnographic variables and subjective assessment of sleep, fatigue, and alertness in patients with DSPS at baseline, after a few weeks of melatonin treatment, and after a few weeks of placebo treatment. To control the first-night effect, which could have caused a "masking effect" (28, 42, 43), we performed two consecutive overnight sleep

TABLE 2. Subjective Assessment of Sleepiness, Fatigue, and Alertness[a]

Measure	Mean	SD	p (vs. baseline[b])	p (vs. placebo[b])	F^c	p^c
Stanford Sleepiness Scale						
Before sleep						
Melatonin	3.5	1.6	>.05	>.05	1.1	NS
Placebo	3.0	1.5	>.05			
Baseline	3.0	1.3				
After sleep						
Melatonin	3.8	1.4	>.05	<.05	5.97	.01
Placebo	4.2	1.5	<.05			
Baseline	3.3	1.0				
Circadian profile score						
Melatonin	3.0	1.1	>.05	>.05	0.73	NS
Placebo	3.3	1.0	>.05			
Baseline	3.3	1.0				
Fatigue scale						
Before sleep						
Melatonin	3.6	1.7	>.05	>.05	0.70	NS
Placebo	3.3	1.6	>.05			
Baseline	3.1	1.5				
After sleep						
Melatonin	3.7	1.4	>.05	>.05	2.70	NS
Placebo	4.2	1.6	>.05			
Baseline	3.4	1.5				
Circadian profile score						
Melatonin	3.2	1.2	>.05	>.05	0.43	NS
Placebo	3.4	0.9	>.05			
Baseline	3.4	1.0				
Composite fatigue score						
Melatonin	10.5	3.2	>.05	<.05	4.5	.02
Placebo	11.5	2.7	<.05			
Baseline	10.8	3.8				
Alertness scale						
ZOGIM-A						
Melatonin	29.0	6.7	>.05	>.05	2.2	NS
Placebo	30.5	6.9	>.05			
Baseline	28.1	6.9				
Circadian profile score						
Melatonin	3.5	1.4	>.05	>.05	0.49	NS
Placebo	3.8	1.0	>.05			
Baseline	3.7	1.2				

[a] Experimental conditions were the same as described in Table 1.
[b] p values for Tukey post hoc analysis.
[c] Overall test for differences.

studies at baseline, after melatonin treatment, and after placebo treatment. In the study conducted by Dahlitz et al.(21), only single-night polysomnographic recordings were made at baseline and after melatonin treatment; no recordings were made after placebo treatment. Furthermore, the report of that study did not provide a rationale for the objective polysomnographic assessment of sleep. Dahlitz et al. (21) reported results for only two sleep variables, SOL and REM onset latency, and excluded other important parameters, such as sleep continuity and sleep architecture. Although our study showed no major impact of melatonin on sleep architecture in DSPS patients, further studies are warranted to investigate the effect of melatonin on the more precise and intrinsic mechanisms involved in sleep architecture, such as the cyclic alternating pattern (44, 45), REM density in different cycles, and REM and slow-wave sleep distribution (46). The possibility of alteration of sleep architecture by means of a dose-response effect cannot be excluded. This is one limitation of our study. Another limitation is that in this article we report sleep measurements obtained only on the second night of polysomnographic study. First-night polysomnographic data are the topic of a separate analysis because a first-night effect, which is usually a normal reaction of healthy subjects to a new and unusual sleep condition, may be present in some patients with psychosomatic disorders, and these pa-

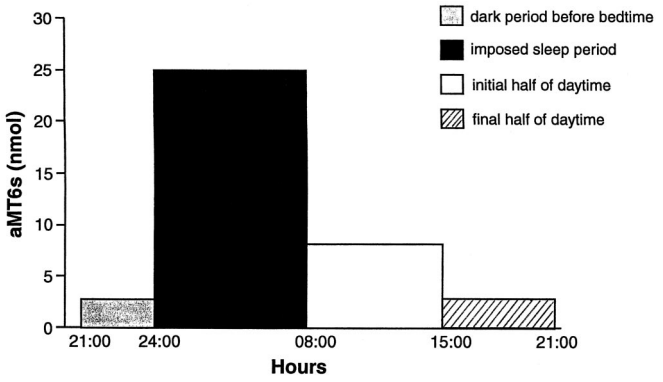

Fig. 2. aMT6s excretion in relation to time of day. The typical nocturnal rise is shown.

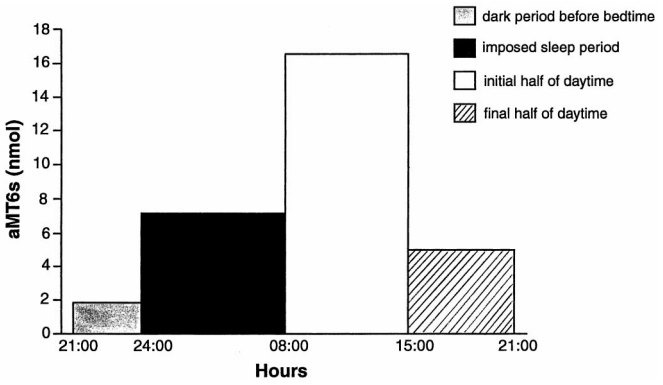

Fig. 3. aMT6s excretion in a subset of five patients with DSPS. An abnormal peak during the initial half of daytime is shown.

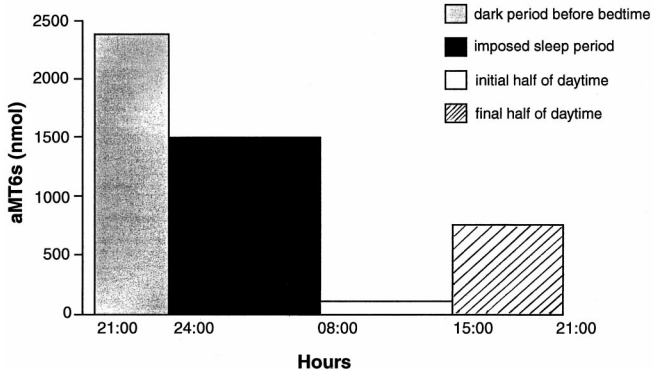

Fig. 4. Normalization of aMT6s excretion in patients with DSPS treated with exogenous melatonin. Note the low levels of aMT6s during the initial half of daytime (cf, Figure 3).

tients may have a better clinical response to treatment (43).

By conventional analysis of our data, we did not find any significant differences in sleep architecture measured at baseline, melatonin treatment, and placebo administration. The standard sleep variables (sleep efficiency, WASO, percentage of sleep stages, etc.) were marked by large interindividual variability and therefore lack the inherent sensitivity to express the intrinsic polysomnographic features.

A salient feature of our study design was allowing patients to select their baseline bedtime and duration of sleep. This strategy permitted us to compare their natural sleep pattern with that of the imposed sleep period (from 24:00 to 08:00 hours) while receiving treatment with melatonin or placebo. Our goal was to evaluate whether melatonin would provide the same or better quality and quantity of sleep in an imposed, socially desirable regimen of the sleep/wake cycle compared with the sleep obtained with the usual delayed regimen that these patients have. Our study failed to reveal any significant difference in TST at baseline and after melatonin treatment (notwithstanding the imposed bedtime in the latter condition). There was a significant decrease in TST after placebo treatment compared with baseline ($p = .006$). Thus, sleep at a phase-advanced, more socially acceptable time was normal in architecture and similar to the phase-delayed sleep of this study group.

In their recent study, Nagtegaal et al. (23) administered melatonin 5 hours before the onset of the evening rise of endogenous melatonin, based on the so-called "dim-light melatonin onset" (47). The authors themselves questioned whether this individualized timing resulted in better clinical effects compared with fixed times of melatonin administration. The partially fixed regimen used in our study allowed patients the flexibility to adjust the phase-setting actions of melatonin. The self-selected timing regimen seems to result in better patient compliance and may be more cost-effective in clinical settings. Furthermore, our findings, which are based on polysomnographic and subjective assessments of sleep, fatigue, alertness, and performance, support a successful entrainment of our patients with DSPS to the socially desirable time of sleep/wake cycle.

Numerous studies have confirmed the nocturnal rise of melatonin production and decline during the daytime in healthy people (7, 15, 17, 18). However, there are no published absolute normative values for aMT6s, and age and sex variations still need to be established (Brown GM, 1999, personal communication). Sack et al. (48) showed that aMT6s decreases with age; however, a recent study by Zeitzer et al. (49) did not support the hypothesis that a reduction in the plasma concentration of melatonin is a general characteristic of healthy aging. There has been considerable debate about the effect of exogenous melatonin on the circadian timing system of endogenous melatonin secretion (50). Although our results do not answer this question per se, we observed a normalization of the

circadian pattern of excreted aMT6s after oral administration of 5 mg of melatonin in three of five DSPS patients who had abnormal melatonin production while taking placebo. These five patients showed peak melatonin excretion between 08:00 and 15:00 hours, and they had the most severe symptoms and manifestations of DSPS as confirmed by both objective and subjective measurements (inability to initiate sleep before 04:00–06:00 hours, loss of employment, and symptoms of comorbid depression). The other 15 patients had the usual nocturnal rise in melatonin production while taking placebo.

Administration of 5 mg of melatonin caused a rapid increase in the amount of excreted aMT6s with the peak during nocturnal hours. Large interindividual differences in excreted aMT6s were observed. The rapid decline of aMT6s from 08:00 to 15:00 hours may explain why our patients did not report any hangover effects, as judged by the subjective assessments of the circadian pattern of sleepiness, fatigue, and alertness. These findings are consistent with previous reports on the effects on the following day (21).

In conclusion, melatonin was an effective treatment for patients with DSPS, as confirmed by both objective and subjective measures. No adverse effects of melatonin were noted during the 4 weeks of treatment. The "phase-advanced" sleep during melatonin treatment significantly decreased SOL compared with placebo but did not alter sleep architecture from that of phase-delayed sleep. However, more controlled observations are required to determine the intrinsic mechanisms involved in the chronobiotic effects of melatonin in DSPS. Dose-response relationships, consequences of long-term use, and the possibility of relapse after discontinuation of melatonin treatment remain to be explored.

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