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Original Article

# Antidepressant action of melatonin in the treatment of Delayed Sleep Phase Syndrome

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ABSTRACT

*Background:* Depression is a common problem in patients with Delayed Sleep Phase Syndrome (DSPS). This study used a randomized, double-blind, crossover, placebo-controlled approach to test the hypothesis that exogenous melatonin (5 mg) can attenuate depressive symptomatology in DSPS patients.
*Methods:* Twenty patients with an established diagnosis of DSPS were dichotomized into DSPS with depressive symptoms (Group I; $n = 8$) and without depressive symptoms (Group II; $n = 12$) based on structured clinical interviews and a score greater than 17 on Center for Epidemiologic Studies Depression Scale (CES-D). Both groups received melatonin and placebo treatment for 4 weeks with a 1-week washout period in between. Participants underwent a clinical interview and psychometric evaluation to assess depression, and overnight polysomnographic sleep studies were carried out at baseline and at the end of melatonin and placebo treatments. Furthermore, melatonin secretion rhythm as a circadian phase marker was assessed by measuring urinary 6-sulphatoxymelatonin levels.
*Results:* Melatonin treatment significantly reduced depression scores in the depressed patients as measured by the CES-D and Hamilton Depression Rating Scale – 17. Melatonin treatment improved sleep continuity in both groups compared to placebo and baseline conditions. Group I individuals showed marked alterations in melatonin rhythms compared to Group II individuals.
*Conclusion:* Exogenous melatonin treatment may be an effective treatment modality for individuals with circadian rhythm sleep disorders and associated comorbid depressive symptomatology.


## 1. Introduction

Depression is often associated with circadian rhythm abnormalities, and many diverse rhythms such as hormone secretion, neurotransmitter secretion and synthesis and behavioral rhythms can be disrupted in depressed patients, suggesting that such disturbances are not unique to a specific rhythm, but instead involve the central circadian pacemaker which regulates the various rhythms [1]. One rhythm that is often disrupted in depression is the sleep-wake cycle, a disruption that, in turn, might lead to other rhythm disturbances [2,3].

Delayed Sleep Phase Syndrome (DSPS) falls under the group of intrinsic Circadian Rhythm Sleep Disorders (CRSD), amongst which DSPS is most common both in general and clinical populations [4,5]. DSPS is characterized by the inability to fall asleep and to awake at conventional times. Sleep onset is usually well past midnight, and sleep offset time is typically past noon [5–7]. When individuals with DSPS are made to conform to earlier retiring times this leads to marked sleep onset insomnia [6,8–10]. DSPS often exhibits psychiatric comorbidities including psychological and functional difficulties such as personality disorders and depression [7,11,12]. DSPS patients may show marked nervousness and lack of control of emotional expression [13]. These characteristics may worsen social withdrawal, causing a loss of social cues in synchronizing their circadian rhythm and a further exacerbation of the circadian problem.

The neurohormone melatonin regulates the timing of the central circadian pacemaker located in the Suprachiasmatic Nuclei (SCN) [14–16]. Significant alterations in melatonin secretion in depressed patients during the acute phase of illness have been documented [17–21]. Stemming from this observation, several strategies have been utilized to manipulate circadian rhythm to alleviate depression [17,22–26]. Exogenous melatonin can modulate the timing of the major sleep-wake episode and have beneficial effects on mood [17,27]. The aim of this study was to investigate the role of exogenous melatonin treatment as a chronobiotic in ameliorating depressive symptomatology in DSPS patients. In addition, we evaluated

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urinary sulphatoxymelatonin (aMT6s) as a marker of circadian phase and the effects of melatonin on sleep in DSPS patients.

## 2. Materials and methods

### 2.1. Study population

Thirteen males aged 35.6 ± 14.0 years and seven females aged 30.8 ± 12.4 years with an established diagnosis of DSPS participated in the study. The following exclusion criteria were applied: shift work, presence of other sleep disorders, age under 16 years, alcohol or drug abuse, current use of psychotropic medications or any other form of medication affecting melatonin secretion, active behavioral treatment, and severe psychiatric and neurological disorders. Prior to inclusion in the study participants were reevaluated based on the International Classification of Sleep Disorders [28], 2-week sleep logs and a clinical interview by a psychiatrist/sleep specialist. The mean bedtime and rising times according to the sleep logs were 02:47 h (range 02:10–06:00 h) and 10:45 h (range 09:30–13:00 h) respectively. The study protocol was approved by the Research Human Ethics Committee of the University Health Network, and all patients signed consent forms prior to being assessed.

### 2.2. Study design

The trial was randomized, double-blind, crossover, placebo-controlled and was conducted over nine consecutive weeks during one season in order to control for seasonal variations in endogenous melatonin levels. Since all patient enrolment and data collection was completed before 2004, the study was not registered as a clinical trial. All patients were divided into two groups based on the presence or absence of comorbid depressive features as judged by a structured clinical assessment, including HDRS-17 [29] and CES-D scale [30]. Patients diagnosed who scored 17 or greater on the CES-D scale were assigned to the group of DSPS patients with comorbid depressive symptoms. Following the clinical interview and psychometric evaluation to assess depression, participants spent two consecutive nights at the sleep clinic for overnight polysomnographic (PSG) sleep studies. Sleep studies were conducted on two consecutive nights to negate a possible confounding effect of the first night [31] on sleep data. This set of psychometric and sleep studies comprised the baseline evaluation. During the baseline sleep studies, participants chose their own retiring and wake up times to be consistent with their normal routines. After the second night of sleep studies, patients were randomly assigned to either the placebo group or the melatonin treatment group. Each participant took 5 mg/day of either melatonin or placebo between 19:00 and 21:00 h (Day 1). Both melatonin and placebo capsules were supplied by Penn Pharmaceutical Limited, UK. Treatment continued for 4 weeks followed by a 1-week washout period prior to treatment crossover. Two-night sleep studies were again conducted on the last two nights of melatonin and placebo treatment (Day 27 and 28; Day 62 and 63).

### 2.3. Sleep physiology measures

The sleep studies after the baseline evaluation had an imposed sleep period from midnight to 08:00 h. The imposed sleep period was used only during the two nights of sleep studies, once while on melatonin and once again during placebo treatment. During the rest of the trial participants were allowed to adhere to their habitual bedtime. Evening exposure to light was not controlled while they were at home during the duration of the study. PSG results obtained on the first night on each occasion were not included in the analysis due to a possible first night effect [31]. A standard montage including electroencephalography, electrooculography, electromyography and respiratory monitoring (oxygen saturation, nasal airflow, and breathing effort) was used. The polysomnographs were scored by a single blinded scorer according to standardized criteria [32]. The sleep parameters included sleep continuity (Sleep Onset Latency (SOL), Total Sleep Time (TST), Sleep Efficiency (SE), and Wakefulness After Sleep Onset (WASO); Arousal Index (AI), sleep architecture (% of each sleep stage; Slow Wave Sleep% in the first and second sleep cycles), and REM sleep details (REM latency; Number of REM episodes) were analyzed.

### 2.4. Psychometric measures

During the initial clinical interview participants were dichotomized based on the presence ($n = 8$) or absence ($n = 12$) of comorbid depressive features and a CES-D score of 17 or greater. This categorization, however, did not affect the order of treatment (melatonin/placebo) received. Both HDRS-17 [29] and CES-D scales [30] were used; the former was completed by the psychiatrist, the latter by patients. Clinical interviews and psychometric evaluations were conducted before the start of the study (baseline) and on the second night of each treatment period (placebo or melatonin) corresponding to the sleep study sessions and the end of each 'treatment' phase.

### 2.5. Circadian profile measures

Urine samples for aMT6s measurements were collected during the 24-h period at 21:00, 03:00, 09:00 and 15:00 h. Urine was collected during placebo treatment for all participants. During the dark period samples were collected under dim light conditions (safe red light less than 5 Lux). Immunoassay for urinary aMT6s was carried out per manufacturer's instructions (CIDtech Research Inc., Ont., Canada).

### 2.6. Data analysis

One-way Analysis Of Variance (ANOVA) was used to determine statistical significance of sleep variables, subjective scores and 6-sulphatoxymelatonin (aMT6s) levels between baseline, melatonin and placebo treatments. Significance based on the ANOVA ($p < 0.05$) was followed by Tukey post-hoc paired comparisons to determine statistically different groups (baseline, melatonin, placebo treatment) using the Statistical Package for the Social Sciences. Results in the text are expressed as mean ± Standard Error of Mean (SEM).

## 3. Results

### 3.1. Melatonin treatment on depression in DSPS

Group I (DSPS patients with comorbid depressive symptoms; $n = 8$) included three women and five men (mean age: 31.5 ± 7.2 years). Group II (DSPS patients without comorbid depressive symptoms $n = 12$) included four women and eight men (mean age: 36.2 ± 15.7 years). The mean scores on the CES-D and HDRS-17 were significantly higher in Group I (33.5 ± 9.4 and 13.2 ± 3.6) than in Group II (13.3 ± 3.6 and 5.6 ± 2.4). While at baseline both scales indicated depression in Group I, after melatonin treatment there was a significant decrease in HDRS-17 (Fig. 1a) and CES-D (Fig. 1b) scores, whereas placebo treatment had no effect on either score (Fig. 1a and b). Changes on the depression scales in Group II were not significant in any limb of the trial (Fig. 1c and d).