

Brief report

## Melatonin treatment of winter depression: a pilot study

Alfred J. Lewy\*, Vance K. Bauer, Neil L. Cutler, Robert L. Sack

*Sleep and Mood Disorders Laboratory, Departments of Psychiatry, Ophthalmology and Physiology / Pharmacology,  
Oregon Health Sciences University, Portland, OR 97201-3098, USA*

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### Abstract

Five patients with winter depression received low doses of melatonin in the afternoon, and five patients received placebo capsules. Melatonin treatment significantly decreased depression ratings compared to placebo. If these findings are replicated in a larger sample with documentation of expected phase shifts, the phase shift hypothesis will be substantially supported. © 1998 Elsevier Science Ireland Ltd.

*Keywords:* Melatonin; Winter depression; Seasonal affective disorder; Melatonin phase response curve; Phase shift hypothesis

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### 1. Introduction

According to the phase shift hypothesis (PSH) of winter depression (WD), bright light exposure should be most antidepressant when scheduled in

the morning [(at which time it causes a phase advance (Lewy et al., 1987)]. Although some studies show no difference between morning and evening light (Meesters et al., 1993; Wirz-Justice et al., 1993; Lafer et al., 1994), most show morning light — and none show evening light — to be more antidepressant (Lewy et al., 1987; Sack et al., 1990; Avery et al., 1991; Eastman et al., 1996; Terman and Terman, 1996). A critical test of the

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\* Corresponding author. Tel.: +1 503 4945635; fax: +1 503 4945329; e-mail: lewy@ohsu.edu

PSH would be to demonstrate an antidepressant effect in these patients using another phase-resetting agent. In our previous attempts to assess the effects of melatonin, we have had difficulties because of its soporific side effect, to which patients with WD appear to be exquisitely sensitive. In the present study, we thought that we might be able to avoid this side effect by administering 0.125 mg at two times 4 h apart in the afternoon. Because melatonin levels would be elevated in the early afternoon and maintained past the time of the endogenous melatonin onset, even this very low dosing regimen should theoretically cause a phase advance (Lewy et al., 1992; Lewy and Sack, 1997).

## 2. Methods

All patients were screened prior to being admitted into the study and must have met the following criteria: (1) the DSM-IV criteria (American Psychiatric Association, 1994) for moderate to severe major depressive disorder (without psychotic episodes) or bipolar disorder (depressed or not otherwise specified) with a winter-type seasonal pattern; (2) scored  $\geq 20$  on the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder Version (SIGH-SAD) (Williams

et al., 1988) with a Hamilton Depression Scale (HAM-D) (Hamilton, 1967) score  $\geq 10$  and an atypical score  $\geq 5$  (Terman et al., 1990); (3) reported that a depression developed during the fall or winter and remitted the following spring for at least the two preceding years; (4) were in good physical health; (5) were not suicidal; (6) were not using psychotropic medications for the prior 4 weeks or other medications that interfered with endogenous melatonin production; (7) did not have other serious psychiatric, medical or sleep disorders; and (8) were not working night shifts. None of the patients had ever used light treatment.

The study was a parallel-group design, consisting of a pre-treatment assessment followed by 3 treatment weeks (Fig. 1), which began in February and ended before the middle of March, 1997. Patients were assigned to either a melatonin or placebo group to counterbalance their initial SIGH-SAD scores and their reported awakening times. For the duration of the study, patients were instructed to maintain a consistent sleep-wake schedule.

Melatonin (0.125 mg, Regis Chemical Co., Morton Grove, IL) or placebo was provided, double-blind, in each of two daily capsules at circadian time (CT) 8 and CT 12, estimated from each patient's initial reported awakening time (which

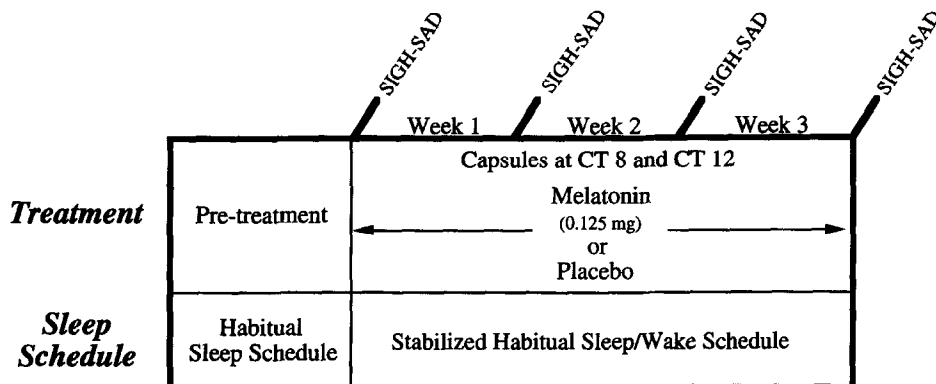


Fig. 1. Experimental design for the study. The study was a 3-week parallel-group design, consisting of a pre-treatment assessment followed by 3 treatment weeks. Patients were assigned to either melatonin or placebo. Melatonin (0.125 mg) or placebo was given in each of two daily capsules at CT 8 and CT 12, estimated from each patient's initial reported awakening time (which was designated CT 0).

was designated CT 0); the average clock times of administration for the melatonin group were 15:18 h and 19:18 h (the placebo group's administration times were 6 min earlier). This treatment regimen was selected in order to use the lowest possible dose that provides an exogenous melatonin pulse from the early afternoon continuous with the endogenous melatonin onset. Although no pharmacokinetic data were obtained in these patients, we were fairly certain from past experience that melatonin levels would remain elevated through the endogenous melatonin onset. All patients were asked by a non-blind investigator if they experienced any sleepiness after taking their first two capsules.

Patients were initially interviewed in person at OHSU using the 29-item SIGH-SAD. Three subsequent interviews were done weekly by telephone. All interviews were conducted by a researcher blind to treatment conditions.

### 3. Results

Ten patients (nine females) with WD were

admitted into the study. The mean age of the melatonin group was 37 years (S.D. = 14; range, 22–58) and the placebo group was 32 years (S.D. = 9; range, 22–42). The mean reported initial wake-up time for the placebo group was 07:12 h; the melatonin group mean was 07:18 h. Mean pre-treatment SIGH-SAD assessments were nearly identical for both groups (29.4 placebo; 29.2 melatonin). Due to interfering school constraints, two patients in the melatonin group dropped out of the study after the second week of treatment. Therefore, the sample size for the third week was too small to be included in the analyses, although it should be mentioned that the mean SIGH-SAD ratings for the third treatment week were identical to those of the first 2 weeks.

A discrete response criterion of  $\geq 39\%$  decrease in SIGH-SAD ratings was selected after plotting the post-treatment ratings against pre-treatment ratings (Fig. 2). By this criterion, which was selected so as to categorize all five melatonin-treated patients as responders, only one out of five patients taking placebo fell into

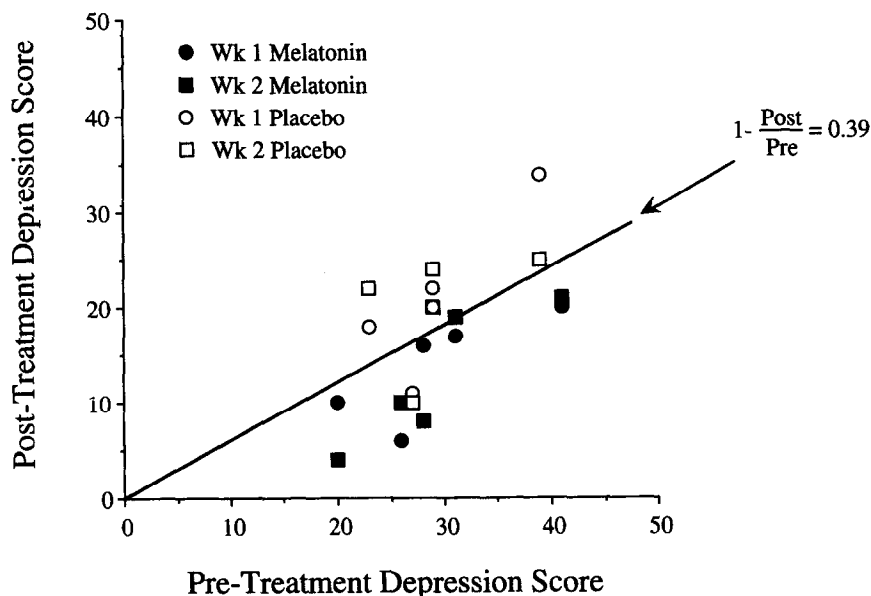


Fig. 2. SIGH-SAD scores (post-treatment vs. pre-treatment) for the melatonin ( $N = 5$ ) and placebo ( $N = 5$ ) groups after 1 and 2 weeks of treatment. Data points on or below the diagonal line indicate a  $\geq 39\%$  reduction in SIGH-SAD ratings and include all of the treated patients but only one patient who received placebo ( $\chi^2 = 6.67$ , Fisher's exact  $P = 0.0476$ ).

this category ( $\chi^2 = 6.67$ , Fisher's exact  $P = 0.0476$ ). This result was probably not influenced by baseline scores which were the same for treated and placebo groups. Indeed, when post-treatment residuals from the fitted regression line were calculated separately for first and second treatment weeks, melatonin/placebo differences were statistically significant (first week unpaired  $t$ -test,  $t = 2.43$ ,  $df = 8$ ,  $P = 0.038$ , two-tailed; second week,  $t = 2.55$ ,  $df = 8$ ,  $P = 0.034$ ).

#### 4. Discussion

Four of the five patients who were taking melatonin reported by telephone interview to one of the non-blind investigators that they could not attribute any sleepiness directly to their capsules; one person (a female, age 58) reported feeling quite tired after taking the afternoon capsule. This patient had also reported feeling tired regularly in the afternoons prior to beginning the study. Thus, to avoid contributing to her afternoon slump, she was told to take the capsules in the evening (when she arrived home and again just before bedtime) for weeks 2 and 3. This patient was the least responsive to melatonin and her ratings increased after the first week; at the end of the study, she was convinced that she had not received melatonin. One patient (a female, age 41, who thought that she was on melatonin but was actually taking placebo) received permission by one of the non-blind investigators to begin treatment with Paxil (50 mg) 2 days before her second treatment week rating. She had the highest post-treatment depression ratings of any patient. It was thought that both of these protocol deviations would, if anything, bias the results against our hypothesis, and so a prospective decision was made not to drop these two patients from the study, because otherwise the sample size would be too small for statistical analyses.

Shortly after beginning capsules, patients were asked whether they thought they were receiving melatonin or placebo. For the melatonin group, one patient thought that she was receiving melatonin, while four did not know. In the placebo group, two people thought they were receiving

melatonin (including our placebo responder) and three did not know.

Circadian phase or pharmacokinetics should be measured in future studies. However, we cannot think of any reason other than a phase advance why afternoon melatonin would be antidepressant in these patients: given that it produces winter-like behavior in animals with seasonal rhythms (Tamarkin et al., 1976), afternoon melatonin would be expected to worsen WD. Indeed, the first use of melatonin in WD was to give low doses from the late afternoon throughout the early morning in order to make patients who were responding to light treatment relapse (this dosing regimen increased symptoms of atypical depression) (Rosenthal et al., 1985). In the only other study of melatonin and WD, administration times were at about 06:30 h or about 23:30 h (Wirz-Justice et al., 1990): 5 mg in this open trial had no effect. In both of these studies, melatonin was administered at times when it would not be expected to cause a phase advance.

Our results are consistent with those of Schlager (1994) who found that a short-acting beta blocker given early in the morning was antidepressant. Schlager was testing the idea that a longer melatonin duration was providing a signal for winter. However, his findings are also consistent with the PSH, in that reduction of endogenous melatonin levels in the morning could result in a phase advance (Lewy et al., 1992). Schlager's findings are also consistent with our observation that patients with WD are very sensitive to melatonin's soporific side effect. Indeed, this hypersensitivity might be related to the pathogenesis of WD, in that these patients who have evidence of phase-delayed circadian rhythms (Lewy et al., 1987; Sack et al., 1990; Avery et al., 1997) might have (their frequently reported) morning hypersomnia because of endogenous melatonin production persisting later in the morning.

If we can demonstrate phase advances with the 'overlap' dosing regimen in this study, there will be broad applications. Under entrained conditions, the phase-advance zone of the melatonin phase response curve (PRC) is in the afternoon and evening (Lewy et al., 1992), when soporific side effects of melatonin should be avoided. Our

dosing regimen (which mimics a sustained-release formulation) allows administration of the lowest possible dose at the earliest possible time in the afternoon, thus potentially maximizing the phase-advance response while minimizing soporific effects. Clearly, the melatonin PRC appears to be useful, as well may be the overlap dosing regimen which provides elevated melatonin levels through the endogenous melatonin onset and which also stimulates the maximal portion of the area under the curve of the appropriate zone of the melatonin PRC.

To those who are tempted by these preliminary data to try treating WD patients with melatonin, we urge caution until these suggestive results are replicated. As mentioned above, these patients appear to be very sensitive to the soporific effect of melatonin. Even with the dosing regimen we have employed in this study, patients need to be warned about this potential side effect.

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