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SECTION 5: TREATMENT STUDIES

5.1 A Placebo-Controlled Trial of Bright Light and Negative Ion Treatment for Chronic Depression: Preliminary Results

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Objectives. Bright light and high-density negative air ion exposure have both shown success in the treatment of seasonal affective disorder (Terman et al., 1998). These nonpharmacologic treatments have fewer side effects and contraindications than antidepressant drugs, and often produce improvement more rapidly. It is conceivable, then, that they would also benefit patients with *nonseasonal* depression who discontinue or cannot tolerate medication use, fail to respond to drugs or relapse while on medication (Kripke, 1998). The present ongoing study extends a pilot trial we previously described (Goel et al., 2001) with addition of an established placebo, low-density negative ions (Terman et al., 1998). *Methods.* Of 32 research volunteers to date, 24 (75%) have been women and eight (25%) men, ages 22–65 (mean age \pm SD, 43.7 \pm 12.4 years), all with Major Depressive Disorder, Single Episode (DSM-IV code 296.2), Chronic (episode duration \geq 2 years). Diagnoses have been with Atypical Features in 21 cases (66%) and with Melancholic Features in eight cases (25%). In order to enter, the Global Seasonality Score must be \leq 6 (in the nonseasonal range) and the patients must be medically healthy and without other Axis I disorders. Subjects were allowed to continue pre-established SSRI antidepressants. The study protocol is the same at both sites (Wesleyan University and the New York State Psychiatric Institute). Patients are being entered throughout the year; thus far, treatment has occurred nearly equally in the spring/summer (Apr.–Sep.; $n = 15$) and fall/winter (Oct.–Mar.; $n = 17$). Patients are randomly assigned to bright light exposure (10,000 lux; $n = 10$), high-density negative air ion exposure (4.5×10^{14} ions/sec; $n = 12$) or low-density negative air ion exposure (1.7×10^{11} ions/sec; $n = 10$). High- vs. low-density ions forms a true double-blind comparison, while light vs. ions forms a single-blind comparison. Treatment is taken at home, daily for 5 weeks, for 1 h within 10 min of waking. Response is assessed weekly using the Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder Version (SIGH-SAD). At entry, the score must be ≥ 20 . We define remission as a pre- to post-treatment reduction in SIGH-SAD score to eight or lower. This interim report applies repeated measures analysis of variance (rmANOVA) with treatment group and season as between-subjects factors to assess differences in SIGH-SAD scores between baseline and the treatment



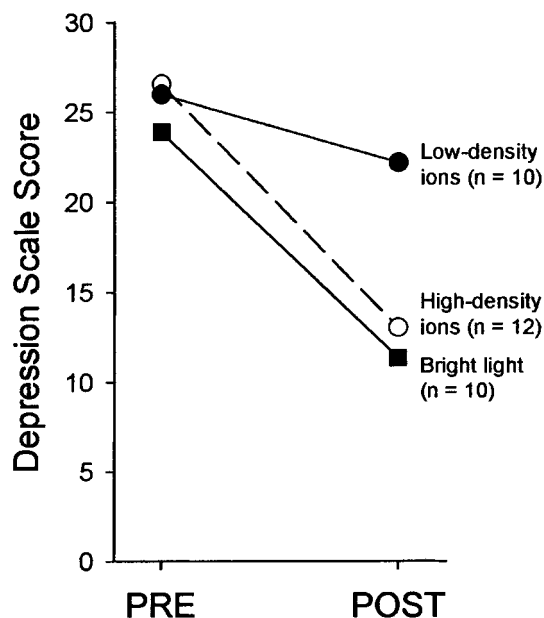


Figure 1.

endpoint at 5 weeks. Post-hoc comparisons assess differences in scores across time and in percentage improvement for each treatment group. The effect size of proportions for patients with remission is expressed as h (≥ 0.8 , large). **Results.** Severity of depression at baseline is closely matched across the three groups (SIGH-SAD grand mean \pm SD, 25.6 ± 4.1 ; see Fig. 1). rmANOVA indicates a significant treatment group \times time interaction ($F_{2,26} = 4.24$, $P < 0.05$). All three groups have shown significant improvement in SIGH-SAD score (light, $t = 5.04$, $P = 0.001$; high-density ions, $t = 5.05$, $P < 0.001$; low-density ions, $t = 2.26$, $P = 0.05$). However, improvement has been far greater for light and high-density ions than for low-density ions. Percentage improvement at week 5 has been similar for the two active treatment groups (high-density ions, $51.1\% \pm 34.4\%$; light, $53.7\% \pm 34.3\%$), in comparison to $16.4\% \pm 22.1\%$ for the low-density ion placebo. This result is mirrored in remission rate [high-density ions, 50% (six of 12 cases); light, 50% (five of 10 cases)], with a large effect size relative to placebo [0% (zero of 10 cases), $h = 1.57$]. Although percentage improvement on the SIGH-SAD has shown no seasonal effect, remission rate for both bright light and high-density ions may be higher in fall/winter, as suggested by the effect size of proportions across seasons (light, $h = 0.87$, $n = 10$; ions, $h = 0.34$, $n = 12$; hypothesis testing will require a larger sample). In both seasons, however, the two active treatments still show large effect sizes ($h > 1.00$) relative to placebo. **Conclusions.** Morning presentation of bright light or high-density negative ions has produced clinical remission in half of our chronically depressed patients, while low-density ions have failed to produce any remission. These response rates, obtained within a controlled trial, are comparable to those seen for winter depression (Terman et al., 1998) and underscore the need for an expanded randomized clinical trial.



Key Words: Light therapy; Negative air ionization; Nonseasonal depression; Nonpharmacologic antidepressants; Placebo.

Support: Research supported by NIH Grant MH42931 (M.T. and J.S.T.) and a Wesleyan Project Grant (N.G.).

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5.2 Bright Light Therapy for Depression During Pregnancy: Preliminary Findings from a Randomized Clinical Trial

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Objectives. Thirteen percent of pregnant women meet criteria for major depression during pregnancy. However, treatment options for the pregnant patient are limited by concern for fetal well-being. While there is overwhelming evidence documenting the efficacy of bright light treatment for seasonal affective disorder (SAD), there is a growing body of literature suggesting its effectiveness in non-seasonal depression (Kripke, 1998). Recent findings from our open-label study show that bright light therapy is a promising treatment for depression during pregnancy (Oren et al., 2002). As an extension of this work, we report here new findings from a double-blind placebo-controlled pilot study. *Methods.* Ten pregnant women with major depression were randomly assigned to a 5-week clinical trial (RCT) with either a 7000 (active) or 500 lux (placebo) 4200K fluorescent light box (modified Healthlight, SphereOne Inc., Silver Plume, CO). Duration of daily light treatment was 60 min to begin within 10 min of morning awakening. At the end of the RCT, subjects had the option of continuing in a 5-week extension phase. The Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder Version (SIGH-SAD) was administered to assess changes in clinical status. Analysis of SIGH-SAD scores for the 5-week RTC was performed with a *t*-test, while analysis across



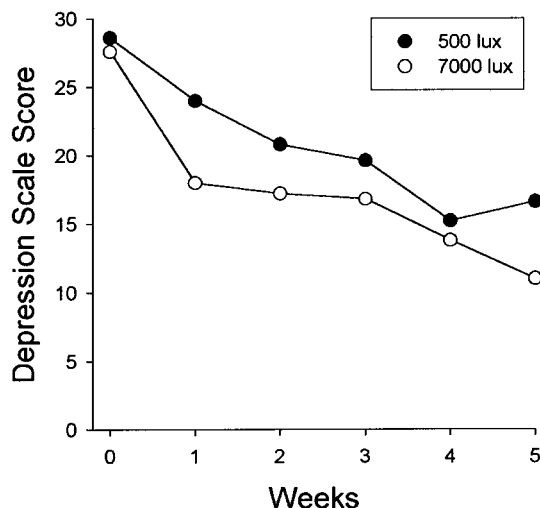


Figure 1.

the 10-week period was performed with a mixed effect linear regression model that tested the significance of assigned condition, with intensity and duration of light as time-dependent covariates and the week of the study as well as the dose \times week interaction. Salivary melatonin was measured according to methods previously described (Terman et al., 2001) and was used to index circadian rhythm phase for comparison with antidepressant results. *Results.* Of the 10 women enrolled, 8 were Caucasian, 1 was African American and 1 was Hispanic. Their mean age was 32.1 years (range, 24–37 years) and mean gestational age was 19.5 weeks (range, 8–32 weeks). There were no significant differences between groups in age or gestational week. Although the presence of seasonality was not exclusionary, only one subject met DSM-IV criteria for the seasonal pattern specifier. Baseline SIGH-SAD scores [mean \pm SD; 27.6 \pm 5.6 (active) and 28.6 \pm 8.7 (placebo)] were not significantly different between groups. Figure 1 shows mean SIGH-SAD score for active (7000 lux) and placebo (500 lux) groups across the 5-week randomized trial. Last observations have been carried forward for missing data and for one subject in the active group who developed hypomania in week 4, but showed relapse when exposure duration was decreased from 60 to 45 min in week 5. Although there was a small group mean advantage of active treatment throughout the RCT, it was not statistically significant at the end of 5 weeks. Three of the subjects who were 5-week non-responders had their light exposure duration increased, or were switched from 500 to 7000 lux light boxes, and became responders by the end of week 10. Thus, in the longer 10-week trial the presence of active vs. placebo light produced a clear treatment effect ($P=0.001$) with an effect size (0.43) similar to that seen in antidepressant drug trials. Successful treatment with bright light was associated with phase advances of the melatonin rhythm. Eight women completed the 5-week RCT and six women completed the 5-week extension phase. Two women dropped out by week 4 due to time-consuming procedures or lack of response, while two women did not qualify for the extension phase because they



had responded to placebo during the 5-week RCT. *Conclusions.* It is unclear whether the efficacy of bright light treatment demonstrated at the end of week 10 is due to enhanced statistical power or adjustments of the daily light dose across the 10-week study. Intriguingly, like for medications, manipulations in light dose could be used to enhance therapeutic response. Dosing of light is flexible, and can be changed daily if there are untoward effects such as hypomania. Although the small sample size in this study dictates cautious interpretation, these findings provide additional evidence for an active effect of bright light therapy for antepartum depression and underscore the need for an expanded randomized clinical trial.

Key Words: Light therapy; Depression; Pregnancy; Melatonin.

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5.3 No Benefit to Using Polarized Rather than Non-polarized Light for the Treatment of Seasonal Affective Disorder

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Objectives. Several animal species can differentiate between polarized and non-polarized ambient light; humans, however, do not have this ability. Honeybees, for example, can detect polarized light, and this aids their navigation. This study was designed to establish whether polarization of artificial light is of importance in the treatment of seasonal affective disorder (SAD) compared to the usual non-polarized light currently used in light therapy (LT) devices. *Methods.* The study was conducted in winter 2001–2002 and 2002–2003 in Novosibirsk, Russia (55°N). Fifteen unmedicated, DSM-IV-diagnosed SAD women (mean ± SEM, 42.3 ± 3.0 years; range, 21–61 years) in the follicular phase of their menstrual cycle (when present), completed two arms of the study including a week of bright white polarized light (6000 lux at a distance of 30 cm from a light box, 45 min each morning) and a week of non-polarized light (6000 lux at a distance of 41 cm, also for



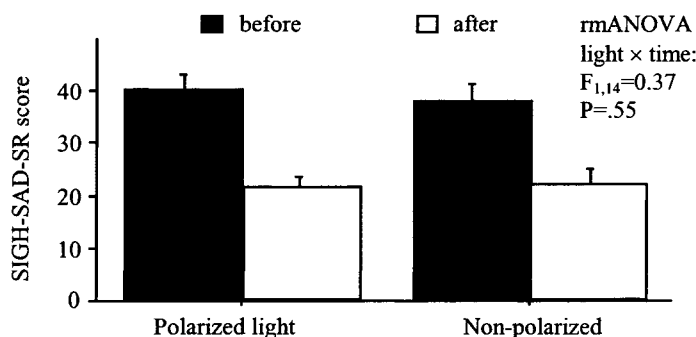


Figure 1.

45 min each morning). Light boxes were modified Outside In Sunray Max with #835 phosphor lamps. Non-polarized boxes were fitted with Outside In's standard K12 pattern UV filtering diffusing screen; light boxes giving circular/reflex polarization were fitted with a special Aura Corporation UK light-polarizing screen. The polarizing screen reduces light transmission; therefore, distances were adjusted to equalize lux levels. The patients were asked to start light treatment shortly after habitual waketime but no later than 1000h. There was a 3-week minimum interval between the two treatments (crossover, counter-balanced order). The self-rating version of the Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder Version (SIGH-SAD-SR) was completed on the day before and day after each of the two sessions. Daily hours of sunlight data were provided by the official meteorological station. The study was single-blind; only the researchers knew treatment assignments. *Results.* There was no difference between the two conditions in SIGH-SAD-SR score reduction (%): 44.2 ± 5.6 for polarized vs. 42.2 ± 6.6 for non-polarized light (see Fig. 1), with a ratio of efficacy of $N = 8 : 7$. The groups did not differ with respect to: initial SIGH-SAD-SR scores (39.9 ± 3.1 vs. 37.5 ± 3.7); expectation ratings for the treatment (2.7 ± 0.3 vs. 2.5 ± 0.2 , possible score between 1 and 5); starting day relative to menstrual cycle onset (5.4 ± 1.4 vs. 6.0 ± 1.2 days); starting time of light treatment during the day (9.0 ± 0.3 vs. 8.9 ± 0.2 a.m.) or sunshine available during the treatment session ($P > 0.42$ in all cases, by either Wilcoxon test or paired *t*-test). There was no effect of treatment order on any of the parameters studied. Response rate ($\geq 50\%$ improvement on the SIGH-SAD-SR) was similar: 7 of 15 cases in polarized light vs. 6 of 15 cases in non-polarized light groups. *Conclusions.* This crossover study revealed no significant difference between using polarized light and non-polarized light in the alleviation of SAD symptoms. The results are consistent with the finding that there is no difference between the effects of these two light modalities on melatonin suppression (Brainard et al., 2000).

Key Words: Seasonal affective disorder; Winter depression; Bright light therapy; Polarized light.

Disclosure: S. B. Hayes of Outside In manufactures and sells the Sunray Max light box.



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5.4 Length of Light Treatment Trial: Does it Influence Outcome?

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Objectives. Original studies of efficacy of light treatment in seasonal depression were 7–10 days in duration. More recently, studies have employed longer durations, in the range of 2–4 weeks, and some have suggested that even longer trials are needed to confirm the efficacy of active bright light over placebo (Eastman et al., 1998). However, historical response rates are generally in the same range for all treatment durations, raising the possibility that expectations regarding the speed of response may influence onset of response. The current pilot study is designed to determine whether subjects respond earlier when randomized to 2 as compared with 5 weeks of light treatment. The potential interaction with intensity was also tested in a preliminary fashion by randomizing subjects to dim vs. bright light. *Methods.* Subjects were consecutive outpatient referrals to our clinics. Subjects were told they would receive either 2 or 5 week of light therapy, with different strengths of light to determine the optimum combination of duration and intensity of light treatment. Subjects were then randomized to receive one of four treatments using a light box with broad band, white fluorescent illumination, with or without a plastic filter (Health Light Inc., Canada): 2 weeks of dim light (<100 lux; “2-dim”); 2 weeks of bright light (10,000 lux; “2-bright”); 5 weeks of dim light (“5-dim”); or 5 weeks of bright light (“5-bright”). Daily 30-min exposure sessions were scheduled in the morning as soon after waking as possible. Subjects were treated at home and kept a detailed log of exposure, sleep and wake times. The Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder Version (SIGH-SAD) was administered at baseline and weekly during the study. For data analysis, the last observation was carried forward for

Table 1.

Time of assessment	Duration of treatment	Responders to different intensities	
		Dim light, <i>n</i> (%)	Bright light, <i>n</i> (%)
At end of study	2 weeks	3 (37.5)	5 (62.5)
	5 weeks	4 (40.0)	3 (42.9)
At end of 2 weeks	2 weeks	3 (37.5)	5 (62.5)
	5 weeks	2 (20.0)	2 (25.0)



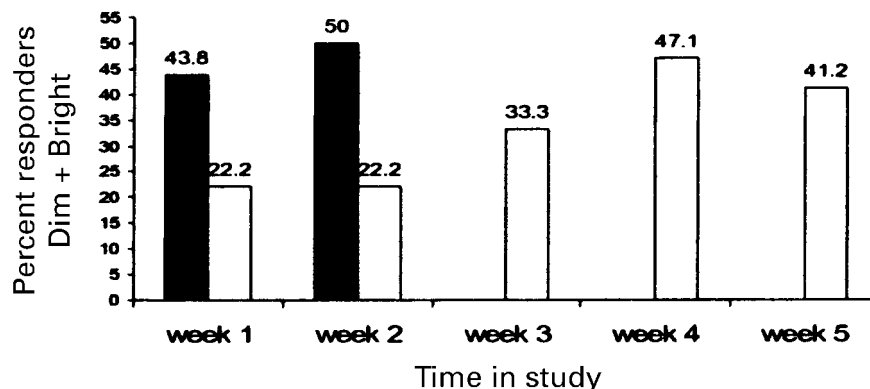


Figure 1.

subjects who received at least 1 day of treatment. *Results.* Thirty-four subjects (mean \pm SD age, 36.2 ± 9.6 years; range, 22–58 years; 52% women) entered treatment (2-dim, $n = 8$, SIGH-SAD score, 31.3 ± 8.1 ; 2-bright, $n = 8$, 29.0 ± 8.6 ; 5-dim, $n = 9$, 28.5 ± 6.2 ; 5-bright, $n = 9$, 27.6 ± 3.2). There were no significant group differences in demographic profile or baseline severity. Three subjects dropped out: one responder in the 5-bright group, one nonresponder in the 5-dim group, and one nonresponder in the 2-bright group. For these subjects, the final SIGH-SAD score was carried forward. Using a 2 (duration) \times 2 (intensity) repeated measures ANOVA at week 2 for both groups, there was no significant main effect of duration, intensity or their interaction on mean SIGH-SAD scores ($\lambda = 0.99$; ns). Results were virtually identical at exit rating for each group. Overall response rate (50% decline in SIGH-SAD score) at the exit rating for all subjects treated with dim light was 38.9% and for all subjects treated with bright light was 53.3% [$\chi^2_1 = 1.0$, ns; effect size (ES) = 0.14; see Table 1]. Response rate for all subjects in the 2-week groups (50%) was not significantly different from that of all subjects in the 5-week groups (41.2%; $\chi^2_1 = 0.1$, ns; ES < 0.1). The response rate at week 2 was greater in the 2-week groups compared with the 5-week groups, under both dim (37.5% vs. 20.0%, ES = 0.19) and bright light (62.5% vs. 25%, ES = 0.38; see Fig. 1 [dark bars, 2-week group]). Remission (final SIGH-SAD score ≤ 9) was not significantly different in the 2-week (30%) vs. 5-week (33%) groups, though there was a trend towards significance in the bright (47%) vs. dim (18%) groups ($P < 0.08$). *Conclusions.* Firm conclusions from this preliminary study are limited by the sample size. There was a general trend toward an overall benefit of bright light over dim light, in keeping with previous studies (for review, see Terman et al., 1989). In addition, we observed a higher rate of response at week 2 in subjects randomized to 2 weeks, as compared with 5 weeks of treatment. We suggest that when subjects are recruited to a light therapy study the speed of response is affected by the length of the trial. The mechanism of such an influence and the possibility that it is also present using other therapeutic modalities requires further investigation.

Key Words: Seasonal depression; Light therapy; Light intensity; Treatment duration.



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5.5 Plasma DLMO₁₀ Zeitgeber Time 14: The Therapeutic Window for Phase-Delayed Winter Depressives Treated with Melatonin

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Objectives. Although causality has not yet been shown, the most recent support for the phase shift hypothesis (PSH) comes from Terman et al. (2001), who have reported on the most impressive correlation to date between the antidepressant response of morning light and the amount of phase advance in clock time of the dim light melatonin onset (DLMO). However, light-induced phase advances of a few hours were found to be therapeutic in patients who are thought to be phase delayed by only about 30 min (Lewy et al., 1998), cases in which no therapeutic window was found as would be predicted by the original PSH. For these longstanding reasons and because of the large nonspecific component of light therapy, we undertook a melatonin treatment study. *Methods.* During each Jan and Feb. of 1999–2002, 100 SAD patients (93 women, 7 men; mean age, 39.7 years; SD = 9.2; range, 20–66 years) took capsules containing either placebo or melatonin (0.225–0.3 mg in 3 to 4 divided doses) every 2h beginning at waketime (defined as zeitgeber time 0, or ZT 0). The morning melatonin group ($n = 33$) took melatonin no later than ZT 6 (and took placebo thereafter) and the evening melatonin group ($n = 33$) took melatonin no earlier than ZT 6 (and took placebo beforehand). The placebo group ($n = 34$) took only placebo. Patients could not tell what was in the capsules. For the baseline week and for 3 weeks of treatment, they were asked to maintain consistent sleep times (according to the weekday habits of each individual), recording them in daily diaries. DLMOs and depression ratings (Structured Interview Guide for the Hamilton Depression Scale—Seasonal Affective Disorder Version; SIGH-SAD) obtained at the end of the baseline week and the third treatment week are reported below. The ZT of the DLMO was calculated by subtracting the average clock time of awakening for the prior week from the clock time of the DLMO. *Results.* Evening melatonin was not significantly more antidepressant than morning melatonin and/or placebo, even though these treatments caused the expected phase shifts. Unlike Terman et al. (2001), we did not detect a significant correlation between the SIGH-SAD percentage change and the phase advance in the clock time of the DLMO. In fact, we did not find statistical significance in any of several correlation analyses using SIGH-SAD scores and clock time of the DLMO. However, if we hypothesize that optimum mood would occur when DLMO ZT = 14 [which is the average of historical controls (Lewy et al., 1998)], our findings uniformly and consistently



support the original PSH, which states that SAD patients who are phase delayed should respond to a corrective phase advance. Patients with a ZT DLMO >14.6 were considered to be the most phase-delayed. In this group, there was a significant correlation between the severity of depression and the amount of phase delay at baseline ($r=0.36$, $P=0.03$). At the end of the third treatment week, a significant correlation remained only when severity of depression was plotted against the absolute difference of the DLMO ZT from the 14-h standard ($r=0.41$, $P=0.01$) or when posttreatment DLMO ZTs <14 were excluded from the analysis ($r\sim 0.35$, $P=0.05$). When posttreatment ZT <4 DLMO ZTs were included, statistical significance was lost; although the sample size was small ($n=6$), these data had a respectable correlation in the opposite direction. At ZTs earlier than 14, SIGH-SAD ratings increased, as predicted, although this correlation was not statistically significant ($r=-0.66$, $P=0.15$). The baseline-to-week-3 drop in depression ratings plotted against the change towards ZT 14 was also statistically significant ($r=0.41$, $P=0.01$). *Conclusions.* These findings support the original PSH, that SAD patients whose DLMOs are phase delayed with respect to wake-time should respond to a corrective phase advance. Patients respond best who have shifted into the therapeutic window, or "sweet spot," defined by a DLMO occurring approximately 14h after wake-time. Further studies are needed to better delineate the phase-delayed group from other SAD patients and perhaps to refine the boundaries of the therapeutic window. Although we did not find an overall treatment effect in patients treated with evening melatonin, some of these patients became overly phase-advanced. Such advances create a circadian mismatch consistent with the longstanding clinical observation that some patients who initially respond to morning light and then begin to relapse do better with less morning light (Lewy, 1987). A phase-delayed DLMO ZT suggests a subsensitivity to light or a longer intrinsic circadian period, both of which are likely to be under genetic control. It would be of interest to re-analyze the data of previous studies using the above assumptions and measures. However, the substantial placebo component to light might obscure the treatment findings. Our data provide continuing support for the recommendation to avoid overly phase-shifting SAD patients (Lewy, 1987).

Key Words: Seasonal affective disorder (SAD); Melatonin; Dim light melatonin onset (DLMO); Circadian rhythm; Phase shift.

Support: Supported by grants from the Public Health Service to Dr. Lewy (R01 MH55703, R01 AG21826 and R01 HD42125) and to the General Clinical Research Center of OHSU (MO1 RR00334), and from the National Alliance for Research on Schizophrenia and Depression (2000 NARSAD Distinguished Investigator Award to Dr. Lewy).

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5.6 Modafinil Improves Winter Depression in a Pilot Study

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Objectives. Hypersomnia and fatigue are cardinal symptoms of seasonal affective disorder/winter depression (SAD/WD). The novel wake-promoting agent Modafinil is thought to work selectively through the sleep/wake centers of the brain to promote wakefulness. Modafinil has been shown to improve wakefulness in a number of clinical models, including narcolepsy and residual excessive sleepiness in patients with obstructive sleep apnea. This open-label pilot study assessed Modafinil as a treatment for SAD/WD. **Methods.** Patients diagnosed with SAD/WD were enrolled in this 8-week, open-label, single-center pilot study conducted during winter months. All patients received oral Modafinil 100 mg in the morning for week 1. For weeks 2 through 8, patients could continue on the 100 mg morning dose or take 200 mg/day of Modafinil as a split dose (100 mg morning, 100 mg midday). Modafinil could be taken as a monotherapy or an adjunct to ongoing, stable antidepressant therapy. Efficacy assessments (weeks 1, 2, 5, and 8) included the Structured Interview Guide for the Hamilton Depression Rating Scale (HAM-D)—Seasonal Affective Disorder Version (SIGH-SAD), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression of Change (CGI-C), Epworth Sleepiness Scale (ESS) and Fatigue Severity Scale (FSS). Efficacy analyses were performed on the intent-to-treat population (ITT; $n = 12$), for whom missing data were estimated by a last-observation carried forward (LOCF) technique. Efficacy variables at all scheduled visits, including the last visit, were compared with the baseline values using the

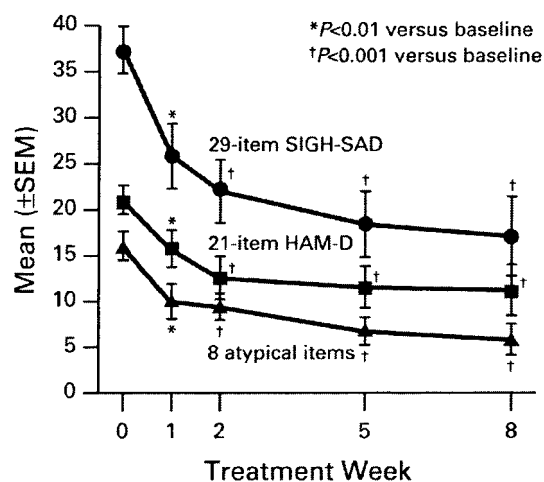


Figure 1.



paired *t*-test for normally distributed data or Wilcoxon signed rank test for non-normal data. The statistical comparison was 2-tailed with a significance level set at 0.05. Response rate was calculated as the percentage of patients completing the study (8 week of Modafinil treatment; $n = 9$) with a $\geq 50\%$ reduction in the SIGH-SAD and the MADRS scores from baseline to week 8. Additionally, we calculated the percentage of patients (ITT, $n = 12$) who had moderate to severe sleepiness (ESS score ≥ 10), fatigue (FSS score ≥ 4), or both (ESS ≥ 10 and FSS ≥ 4) at baseline and at week 8 or last visit. Patients receiving at least 1 dose of study drug were included in the safety analysis ($n = 13$). Adverse events and vital signs were monitored. **Results.** Thirteen patients (11 women, 2 men; mean age, 41 years) were enrolled, 12 (92%) could be evaluated for efficacy, and 9 (69%) completed treatment (8 weeks). Daily Modafinil dose (weeks 2 through 8) was 100 mg for five (42%) and 200 mg for seven (58%) patients. Six patients were taking only Modafinil, while six were also taking an antidepressant. Modafinil significantly improved SAD/WD as shown by reductions from baseline in mean SIGH-SAD (see Fig. 1) at week 1 ($P < 0.01$) through week 8 ($P < 0.001$ weeks 2 through 8) and MADRS total scores from week 2 through week 8 ($P < 0.01$ for all). At week 8, mean SIGH-SAD total score was 17.1 (vs. 37.2 at baseline, $P < 0.001$) and mean MADRS total score was 13.3 (vs. 26.9 at baseline, $P < 0.01$). Modafinil significantly improved overall clinical condition (CGI-C) at all time points ($P < 0.001$). The response rate was 67% (6/9) on the SIGH-SAD (29-item), HAM-D (21-item), and MADRS, and 100% (9/9) on eight atypical SIGH-SAD items. Modafinil significantly improved wakefulness. Mean \pm SD ESS scores were 13 ± 4.1 at baseline, 9.1 ± 2.8 at week 2 ($P < 0.01$) and 8.0 ± 3.3 at week 8 ($P < 0.01$). Modafinil also significantly reduced fatigue. FSS scores were 5.3 ± 0.9 at baseline, 4.6 ± 0.8 at week 2 ($P < 0.01$) and 3.9 ± 1.3 at week 8 ($P < 0.01$). Modafinil reduced the percentage of patients ($n = 12$) who had both moderate to severe sleepiness (ESS ≥ 10) and moderate to severe fatigue (FSS ≥ 4) from 75% at baseline to 17% at week 8. Modafinil was well tolerated. The most common adverse events were headache (38%), dry mouth (30%) and dyspepsia (23%). **Conclusions.** Modafinil may be an effective and well-tolerated treatment in patients with SAD/WD. Interpretation of the current results must consider that this study enrolled a relatively small number of patients at a single site who received open-label Modafinil. In the absence of a placebo control, the occurrence of some degree of spontaneous remission cannot be excluded. Moreover, it is not possible to determine if Modafinil improved SAD/WD due to a direct effect on mood or, more likely, if the positive overall response was secondary to the known effects of Modafinil on wakefulness and fatigue. Further controlled trials are warranted.

Key Words: Modafinil; Seasonal affective disorder (SAD); Winter depression; Wakefulness; Fatigue.

Support: This study was supported by Cephalon, Inc., West Chester, PA, USA. **Prior presentation:** This abstract is expanded from Lundt (2003).

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5.7 Cognitive-Behavioral and Light Treatments for Seasonal Affective Disorder: Interim Analyses from a Controlled Randomized Clinical Trial

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Objectives. We previously piloted a novel, cognitive-behavioral therapy (CBT) for winter seasonal affective disorder (SAD). Cognitive-behavioral therapy alone, light therapy alone (LT), and their combination (CBT + LT) significantly improved acute SAD symptoms with no differences between the treatments (Rohan et al., in press). At our 1-year follow-up, CBT, particularly in combination with LT, appeared to have significant prophylactic benefits over LT alone regarding symptom severity and relapse rates. Given these promising preliminary findings, we initiated a controlled, randomized clinical trial to further test our CBT and to rule out alternate explanations for the treatment effects. Here, we report interim results for treatment completers over the first 2 years of our ongoing study. **Methods.** Community adults who met DSM-IV criteria for Major Depression, Recurrent, with Seasonal Pattern and Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder Version (SIGH-SAD) criteria for a current depressive episode were randomly assigned to 1 of 4 6-week conditions: CBT, LT, CBT + LT, or a minimal contact/delayed light therapy control group (MCDT). Cognitive behavioral therapy was conducted in a group format for 1.5-h sessions twice a week, and followed our manual. Light therapy was initiated using a 10,000-lux light box in 2 45-min doses in the morning (0600–0900h) and evening (1800–2100h). Our choice for a split-dose regimen was based on a recent meta-analytic finding of greater effect sizes for morning-plus-evening light's effectiveness relative to morning or evening light alone (Lee et al., 1997). Subsequently, the 1.5-h duration remained standardized, and the time of day for light administration was individually adjusted to maximize response, address evident phase shifts, and reduce side effects. CBT + LT encompassed all elements of the CBT and LT regimens. Minimal contact/delayed light therapy control group participants received light therapy after a 6-week delay with weekly symptom monitoring. All treatments were completed by the first week in March. Outcome was assessed using the SIGH-SAD, administered by two blind raters with inter-rater reliability >0.90, and the Beck Depression Inventory-Second Edition (BDI-II). **Results.** Of the 46 participants recruited, six dropped out after qualifying and an additional four dropped out after randomization (1 CBT, 2 LT, 1 MCDT). Completers ($n = 36$) were predominantly middle-aged (mean \pm SD, 45.6 ± 11.0 years), Caucasian (83.3%) women (88.9%). 4 (Treatment group) \times 2 (Occasion: pre- and posttreatment) ANOVAs revealed a Group \times Occasion interaction on both the SIGH-SAD, $F_{3,32} = 3.36$, $P = 0.031$, $\eta^2 = 0.239$, and the BDI-II, $F_{3,32} = 3.25$, $P = 0.035$, $\eta^2 = 0.233$. Follow-up simple main effect analyses and Tukey's post-hoc comparisons revealed that CBT and CBT + LT improved SIGH-SAD scores more than MCDT; however, LT and MCDT did not differ at posttreatment. In contrast, CBT, LT, and CBT + LT all improved BDI-II scores relative to MCDT. On both dependent measures, the three active treatment groups improved over treatment, whereas MCDT did not. **Conclusions.** Although promising, these interim analyses provide only a descriptive update on our progress, and final results are not expected until the trial's completion. If these findings and



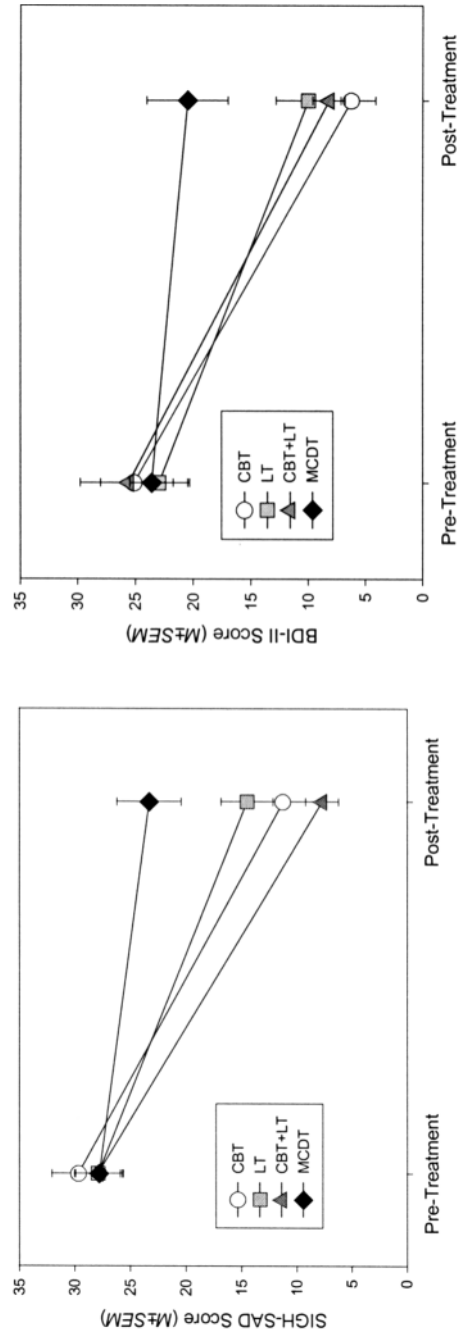


Figure 1.



our pilot study results (Rohan et al., in press) are replicated as our trial continues and achieves sufficient power, the nearly half of SAD patients who do not remit with light therapy alone (Terman et al., 1989) may possibly benefit from CBT as a supplementary or alternative treatment, particularly for maximizing long-term outcome and preventing relapse.

Key Words: Cognitive-behavioral therapy; Light therapy; Seasonal affective disorder.

Support: Grants 1 R03 MH0659 from the National Institute of Mental Health and C072EJ from the Uniformed Services University of the Health Sciences (USUHS). The opinions and assertions expressed herein are those of the authors and are not to be construed as expressing the views of the USUHS or the United States Department of Defense.

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Note: The following abstract does not appear in the published collection (*Chronobiol Int* 2003;20:1149-1221), and should be cited as appearing in *Soc Light Treatment Biol Rhythms Abst* 2003;15:73-74.

5.8 Delayed Sleep Phase Syndrome: Effects of Isolated or Combined Use of Melatonin and Light Therapy

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Objectives. Delayed sleep phase syndrome (DSPS) involves undesirably late bedtimes and rise times, with extreme difficulty falling asleep and waking up early. DSPS patients have been treated with bright light in the early morning or melatonin late at night. The current study evaluated – through a randomized, double-blind protocol – the effects of 4 weeks of treatment with bright light (BL) or melatonin (MEL) alone, or in combination, on sleep onset time (SOT), melatonin onset and the core body temperature nadir. *Methods.* Participants were 20 patients diagnosed with DSPS according to the ICSD (Diagnostic Classification Steering Committee, 1990), 12 men and 8 women, 21 to 64 years of age. They were randomly assigned to 3 groups: (1) BL, 10,000 lux in the morning + placebo pill at night; (2) MEL, 900 lux in the morning + melatonin (3mg) at night; and (3) BL+MEL, 10,000 lux in the morning + melatonin at night. They were asked to avoid naps and to wake up no later than 2 hours after their baseline body temperature nadir. Measures included 24-h rectal temperature (recorded in 1 min intervals) and plasma melatonin concentration (blood samples taken at 30 min intervals from 1800-0900h under light levels around 50 lux, and at 60 min intervals from 0900-1800h under light levels \leq 400 lux). Profiles were determined before and after the treatment phase during winter in the southern hemisphere. SOT was determined by actigraphy. The core body temperature nadir was estimated by cosinor analysis, and melatonin onset was defined as the time at which plasma concentrations rose above 10 pg/ml. Light therapy sessions lasted 30 min and were scheduled within 2 hours after each individual's baseline body temperature nadir. Placebo or melatonin pills were given 5 hours before the usual bedtime of each patient, as determined at baseline. The typical baseline rise time was around 1000h and bedtime was around 0230h. Considering rise time as CT 0, melatonin administration was between CT 11 and CT 12, which lies in the phase-advance portion of the melatonin phase response curve. Group comparisons were tested from baseline to posttreatment using a 2-way ANOVA with repeated measures for the time factor, followed by Newman-Keuls tests. *Results.* The SOT showed a significant advance in all groups ($P < 0.001$), with no differences among groups. The treatments did not change the time of melatonin onset or the core body temperature nadir (Table 1). *Conclusions.* These data suggest that the combination of bright light and melatonin does not provide any extra benefit to DSPS patients. However, high intragroup variability may have obscured differential treatment effects (two patients showed phase delays of melatonin onset, and two others showed phase delays of the temperature nadir). An advantage of combined treatment might be observed using a larger sample size.

Key Words: Delayed sleep phase syndrome (DSPS); Bright light therapy; Melatonin onset; Core body temperature; Actigraphy.

Support: Fundação de Amparo à Pesquisa do Estado de São Paulo, and Associação Fundo de Incentivo à Psicofarmacologia.

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Table 1.

	BL (n = 7)	MEL (n = 6)	BL+MEL (n = 7)
Sleep Onset Time			
Baseline	02:54±1:29	02:19±0:42	02:35±0:54
Posttreatment	01:07±1:24*	00:45±1:27*	01:24±1:17*
Melatonin Onset Time			
Baseline	23:44±2:05	00:02±3:14	23:17±1:58
Posttreatment	22:33±1:35	22:18±0:53	23:42±1:42
Temperature nadir			
Baseline	07:36±1:42	05:27±1:46	07:35±2:05
Posttreatment	07:16±1:39	04:25±2:11	06:24±2:25

Data (hh:mm) expressed as mean±SD.

* $P < 0.05$, different from the corresponding baseline condition.