Light Therapy for Seasonal Affective Disorder with Blue Narrow-Band Light-Emitting Diodes (LEDs)

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Background: *While light has proven an effective treatment for Seasonal Affective Disorder (SAD), an optimal wavelength combination has not been determined. Short wavelength light (blue) has demonstrated potency as a stimulus for acute melatonin suppression and circadian phase shifting.*

Methods: *This study tested the efficacy of short wavelength light therapy for SAD. Blue light emitting diode (LED) units produced 468 nm light at 607 $\mu W/cm^2$ (27 nm half-peak bandwidth); dim red LED units provided 654 nm at 34 $\mu W/cm^2$ (21 nm half-peak bandwidth). Patients with major depression with a seasonal pattern, a score of ≥20 on the Structured Interview Guide for the Hamilton Depression Rating Scale-SAD version (SIGH-SAD) and normal sleeping patterns (routine bedtimes between 10:00 pm and midnight) received 45 minutes of morning light treatment daily for 3 weeks. Twenty-four patients completed treatment following random assignment of condition (blue vs. red light). The SIGH-SAD was administered weekly.*

Results: *Mixed-effects analyses of covariance determined that the short wavelength light treatment decreased SIGH-SAD scores significantly more than the dimmer red light condition ($F = 6.45$, $p = .019$ for average over the post-treatment times).*

Conclusions: *Narrow bandwidth blue light at 607 $\mu W/cm^2$ outperforms dimmer red light in reversing symptoms of major depression with a seasonal pattern.*

Key Words: Seasonal Affective Disorder, wavelength, blue, circadian, light therapy, LED

Although the pathophysiology of Seasonal Affective Disorder (SAD) remains uncertain, studies of bright white light-induced melatonin suppression in humans led directly to showing that light could be used therapeutically to treat winter depression (Lewy et al 1980 1982; Rosenthal et al 1984) and phase shift circadian rhythms (Czeisler et al 1986; Lewy et al 1987). Further studies suggested a link between circadian regulation, melatonin and SAD, as it was determined that light not only acutely suppressed melatonin and entrained the circadian melatonin rhythm, but also elicited changes in the duration of elevated melatonin production relative to photoperiod length (Wehr et al 1993). Lengthened duration of elevated nocturnal melatonin secretion during the winter nights has been implicated as an underlying physiological seasonal change associated with the pathology of winter depression (Wehr et al 2001). In addition, some studies have shown that clinical improvement with light therapy correlates with the phase shifts induced (Lam 1998). One experiment demonstrated the superiority of morning versus evening light treatment along with evidence of phase-delayed circadian rhythms in SAD patients via dim light melatonin onset (DLMO) measurements (Lewy et al 1998).

Spectral characteristics of light have been shown to influence the amount of light needed to suppress melatonin (Brainard et al 2001a, 2001b; Thapan et al 2001). These action spectra show a spectral peak sensitivity in the blue portion of the spectrum (446–477 nm) and fit a vitamin A_1 retinaldehyde opsin template, suggesting that the principal photic input to the retinohypothalamic tract is mediated by a novel photoreceptor system. In addition, a selective comparison of 460 versus 555 nm monochromatic light showed shorter wavelength blue light to be significantly more potent than the longer wavelength green light for circadian phase shifting (Lockley et al 2003). Testing the efficacy of these wavelength regions in the treatment of SAD may help to further determine the optimal wavelength for light therapy.

Standard light treatment generally has been administered via a light box at ~10,000 lux every morning after awakening, for approximately 30 to 60 minutes (Lewy et al 1998; Eastman et al 1998; Terman et al 1998, 2001; Desan and Oren 2001). These light sources typically produce broad bandwidths of polychromatic white light, with great variability in the balance of wavelengths emitted across the spectrum (Brainard 1998). Side effects sometimes associated with current white light treatment include hypomania or agitation, insomnia, headache, eye or vision problems, nausea or vomiting, dizziness, anxiety or feeling "wired," sedation and tightness in chest (Labbate et al 1994; Kogan and Guilford 1998; Terman and Terman 1999). These effects may be the result of light intensity, phase advances caused by morning light treatment, or other factors. Side effects of light treatment are relatively infrequent and benign compared to those of pharmacological treatments, and they generally remit spontaneously or with reduction of light intensity or exposure time (Oren and Rosenthal 1992; Kogan and Guilford 1998). Employment of optimal wavelengths in treating SAD, however, may elicit therapeutic benefit with lower light intensities and/or shorter duration of exposure. These developments may result in reduction of some side effects, increased ease of use, and enhanced comfort and compliance.

Determining specific lighting parameters and exposure techniques for light therapy has been an area of particular interest. Broad-spectrum white fluorescent light and cool white fluorescent light were found to be equally effective (Bielski et al 1992). Broad-spectrum white light, both with and without UV emission, equivalently reduced SAD symptoms (Lam et al 1991). Those findings permitted the elimination of UV from light treatment devices, increasing safety and minimizing risk of possible UV toxicity in SAD patients. Treatment efficacy for SAD was compared in three different fluorescent light conditions with different

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spectral power distributions, and broad spectrum white light was found to be more effective than equal photon doses of red and blue light (Brainard et al 1990). Additional studies showed green fluorescent light to be therapeutically more potent than an equal photon dose of red fluorescent light (Oren et al 1991). A later meta-analysis reported that red wavelengths are relatively ineffective in the treatment of SAD while short and medium wavelengths of visible light produced antidepressant effects (Lee et al 1997). In some of the studies reviewed, however, red light was studied at dimmer intensities than was light of other wavelengths.

The relative ineffectiveness of dim red light has enabled SAD researchers to use it as a control when examining the effectiveness of various light sources. Due to limitations in technology when earlier studies of wavelength efficacy were completed, the half-peak bandwidths of light sources were considerably large, with significant peaks throughout the spectral distribution curves (Brainard et al 1990; Oren et al 1991; Stewart et al 1991). With the technological advancements in light emitting diodes (LEDs), the production of new light treatment equipment with much narrower bandwidths of light and the convenience of portability is now possible (Craford et al 2001). LED technology enables more accurate and precise efficacy studies of different wavelengths of light in the treatment of SAD.

Photobiological safety is always a concern when employing a new light therapy device (Waxler et al 1992; Remé et al 1996). In particular, photochemical damage of the retina may occur due to overexposure to short-wavelength visible light (Grimm et al 2001). The 435–445 nm wavelength region is hazardous at high intensities, with the potential hazard dropping rapidly with increasing wavelength (American Conference of Governmental Industrial Hygienists [ACGIH] 2003). The LED light tested in this study emitted narrow-band blue light with a concentration of energy at 468 nm, with the majority of light energy of a longer wavelength than the peak sensitivity of phototoxicity (see Figure 1). An independent hazard analysis of the red and blue units is described below.

A melatonin suppression test was performed with the prototype LED panels as a prelude to studies of treatment efficacy for winter depression (Glickman et al 2003). This study showed that the mean percent change in melatonin was significantly stronger for exposure to blue LED light at 500 $\mu W/cm^2$ (−34%) compared to red LED light at 15 $\mu W/cm^2$ (+14%) or the dark control condition (+28%) in healthy female subjects. Similar, but modified, LED panels were then used in the following study to test the hypothesis that narrow band short wavelength LED light is effective in the treatment of SAD by comparing it to treatment with dim red light.

Methods and Materials

Light Treatment Devices

The light units designed and produced for this study each consisted of an LED array of 276 LEDs mounted behind a plastic lens diffuser, housed within 20 by 24 cm panels (Apollo Light Systems, Orem, Utah). The spectral power distributions of these light boxes had no overlap in wavelength emission, as illustrated in Figure 1.

The spectral power distributions were measured with a Fieldspec A103000 spectroradiometer (Analytical Spectral Devices, Boulder, Colorado). The information in Table 1 shows the calculated radiometric and photometric characteristics of the three light therapy devices illustrated in Figure 1.

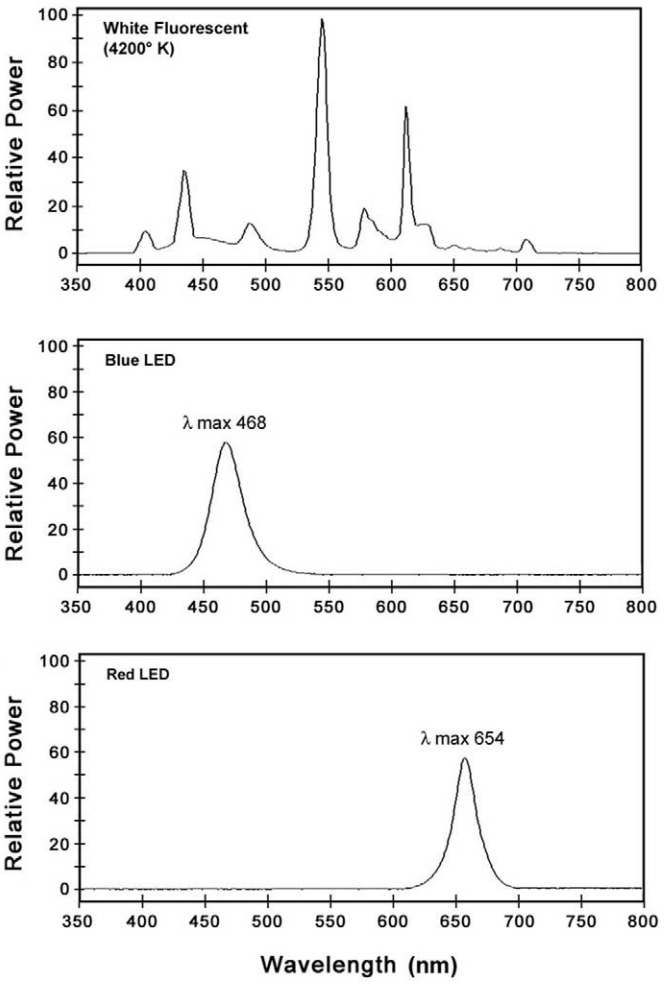

Figure 1. These graphs illustrate spectral power distributions (SPD) of three different light panels. For ease of comparison, each of the SPDs has been normalized to illustrate its relative power. The top graph represents a sample SPD from a commercially available, standard white fluorescent light panel that emits light across the spectrum broadly, with multiple peaks. The SPDs of the two LED panels designed for this study are depicted in the bottom graphs. In contrast to the top graph, these SPDs demonstrate narrower bandwidth lights, with single respective peaks at 468 nm and 654 nm. In addition, the absence of any spectral overlap between the two experimental LED panels is clearly depicted. Radiometric and photometric data for these three light sources are provided in Table 1.

Slight variations in luminous intensity and peak spectral outputs of LEDs are due to the LED manufacturing process (Rea 2000). Among the LED devices constructed for this study, variances of 2 and 5 nm were measured in the red and blue LEDs, respectively. The white fluorescent unit, of the triphosphor type, is a standard array of fluorescent tubes covered by a plexiglass diffusing screen that absorbs UV light. Spectral power distribution of this unit shows three wavelength peaks between approximately 425 and 645 nm.

Hazard Analysis

Before patients began light treatment trials, an independent hazard analysis following the current accepted national and international guidelines was applied to each LED light source (International Commission on NonIonizing Radiation Protection [ICNIRP] 1997; American Conference of Governmental Industrial Hygienists [ACGIH] 2001; American National Standards Institute

Table 1. Radiometric and Photometric Comparison of Fluorescent and LED Light Panels

Therapeutic Device/Distance from Meter	Spectral Characteristics	Irradiance ($\mu W/cm^2$)	Photon Density (photons/cm^2/s)	Illuminance (lux)
4200°K Fluorescent/59 cm	Broad Bandwidth 390–715 nm Multiple peaks	2664	7.30×10^{15}	10,000
Blue LED/50 cm	Narrow Bandwidth λ_{max} = 468 nm 27 nm FWHM	607	1.43×10^{15}	398
Red LED/50 cm	Narrow Bandwidth λ_{max} = 654 nm 21 nm FWHM	34	1.13×10^{14}	23

Fluorescent and LED (light emitting diode) light sources are described in terms of spectral characteristics (nm [nanometer] range for fluorescent device and, for LEDs, peak nm readings and FWHM [full width half max] ranges). Irradiance is measured in microwatts per centimeters squared, Photon Density in photons per centimeters squared per second, and Illuminance in lux.

and Illuminating Engineering Society of North America [ANSI/IESNA] 1996). These standards are available from the publishers indicated in the references. This analysis used the Model 1400A Radiometer/Photometer (International Light, Newburyport, Massachusetts), with two different detectors: 1) a Model SEL240 detector with input optic T2ACT3 that had been calibrated to read directly in terms of the ACGIH/ICNRIP UV-Hazard effective irradiance; and 2) a broad-band visible-near-infrared radiometer detector head, Model SEL003 detector with Input Optic W#6847 and Filter F#14299 calibrated to measure irradiances between 380 and 1000 nm and utilized to measure photoretinitis, or "blue-light" hazard. A radiance hood limited the field of view of the detector to .45 steradian (sr) and was used to directly measure the radiance of the sources. In addition, a luminance meter (Minolta Corp., Osaka, Japan) was employed to measure the panel luminance as a check of radiance measurements. Although the study anticipated a viewing distance of 50 cm, light safety was assessed at shorter distances as well, including at the panel surface (0 cm). The Food and Drug Administration's Center for Devices and Radiological Health reviewed the full report and concurred with the analysis and findings, based on the radiological measures provided; this opinion, however, did not imply that an Investigational New Drug (IND) status had been granted.

Subjects

Patients with major depression with a seasonal pattern according to the Diagnostic and Statistical Manual-IV (DSM-IV), a score of ≥20 on the Structured Interview Guide for the Hamilton Depression Rating Scale-SAD version (SIGH-SAD) (Williams et al 1994) and normal sleeping patterns were recruited during the winter of 2003–2004 from clinic patients and media advertising. Subjects were required to have a routine bedtime starting between 10:00 pm and midnight and a wake time that would allow for a 45-minute light treatment period between 6:00 and 8:00 am. The absence of medical confounds as well as freedom from photosensitizing conditions and/or any of 13 photosensitizing pharmacological agents for each patient was determined through a medical examination. In addition, normal thyroid functioning, the absence of substances of abuse and establishment that women of childbearing age were not pregnant was confirmed via blood and urine analysis. Patients were not excluded from the study if they were taking psychotropic medications as long as dosage had been stable for ≥6 weeks and there were no dosage changes for the duration of the study. Patients were not included if they had been using a light therapy device within 3 weeks or less of the study. In addition, patients were excluded if they had any additional major psychiatric disorder or medical illness that could affect their mental state, compliance with the study protocol, or ocular and dermatological health.

Study Protocol

A three-week parallel design study of outpatient treatment with short wavelength narrow-band LED light therapy was conducted. The planned sample size was 30. The treatment period was confined to the fall/winter season, with all light treatment between October 10, 2003 and March 17, 2004. Prior to participation, all subjects signed an Informed Consent form approved by the Thomas Jefferson University Institutional Review Board. After completion of all preliminary screening, patients were randomly assigned one of the LED light box units–either the short wavelength blue LED light panel or the long wavelength dim red LED light panel–and received detailed instruction on how and when to utilize the light. Patients were told that the study was designed to determine the effectiveness of SAD treatment lights of specific colors and that there was a possibility that they would be given a treatment condition that was ineffective. Patients were shown how to operate the light panel and, after sitting briefly in front of and at a 50 cm distance from the light assigned to them, rated expectations of efficacy on a scale of 0–5 (0 = not helpful; 5 = complete remission of SAD symptoms).

Patients then were assigned a three-week outpatient treatment period of morning light therapy, for 45 min daily between 6:00 and 8:00 am. They were instructed to sit directly in front of the light panel, with its center at ~50 cm from their eyes, and to glance at the light for a few seconds approximately every minute. Patients also were required to keep a log of sleep, wake and treatment times throughout the study period as well as to phone in reports of wake-up and light treatment times immediately after completion of each daily treatment. Patients not calling in were phoned. This daily correspondence provided patients with an opportunity to seek advice on light treatment use and to report any adverse experiences or concerns. SIGH-SAD scores were assessed weekly for each patient by the same rater, who was blind to condition. Side effects profiles were not a planned focus of the study, but at each weekly assessment patients were asked specifically if they had noted any side effects or problems due to the light treatment.

Statistical Analysis

The SAS System Version 8.2 (SAS Institute, Inc., Cary, North Carolina) was employed for statistical analysis. The primary analysis was a repeated measures analysis of covariance (ANCOVA), with baseline SIGH-SAD score as covariate. Subjects

nested within experimental condition were included as a random effect. An unstructured covariance structure for the within-subject component of variance was used, thus allowing that the within-subject variability varied with time. Analyses were done with SAS Proc Mixed. Prior to final analyses, two steps were taken. First, residuals were examined for reasonableness of the normality assumption. The distribution of residuals was symmetric, so no transform was used for the dependent variable. Second, it was considered whether the variances varied with either condition or sex. For this, Akaike's information criterion was used, without regard to impact on the results to be reported. It was found that the within-subject variances did differ by sex, with larger variances for women. All reported results allow this sex difference in variances. Satterthwaite's approximation was used for degrees of freedom. An unpaired *t*-test was used to analyze expectation scores between conditions. Primary treatment effects reported are based on the main effect of treatment. Thus, they represent the difference between treatments averaged over the post-baseline measurement times.

Results

Hazard analysis confirmed that no potential hazardous ultraviolet radiation was emitted from the surface of the light panels. The effective irradiance was less than .05 $\mu W/cm^2$ and, therefore, well below the ACGIH/ICNIRP exposure guideline of .1 $\mu W/cm^2$. In addition, the blue light panel was found to operate at emission levels far below limits recognized as maximal safe exposure limits, at less than 15% of the limit (even for patients using photosensitizing drugs) for even the most potentially dangerous visible wavelengths of 435–445 nm. The Food and Drug Administration was provided with the full report and confirmed the assessment, based on the radiological measurements provided.

Twenty-six patients were entered into the study, and 24 patients completed two or more weeks of light treatment (mean age ± SE; 44.38 ± 2.62 years; age range 25 to 70 years). Of the two patients not completing the study, one did not begin light treatment, reporting schedule conflicts for using the light box in the designated time frame. Another patient withdrew from the study after one week without improvement in symptoms. Both of these patients had been assigned the blue LED light condition. One subject in the blue light group had to withdraw from the study before starting week three of the trial since his primary physician put him on a photosensitizing medication; his scores for week two were used as his final scores. This resulted in a total of 71 post-treatment measurements from 24 subjects. Four subjects in each group had been taking antidepressants. These medicated subjects, however, met the same SCID criteria (First et al 2001) as did unmedicated subjects for major depression, and we have not differentiated them in data analysis. Eleven subjects completed light treatment with the blue light condition (9 females, 2 males), and 13 completed the dim red light condition (10 females, 3 males). Two subjects, each assigned to a blue light unit, missed seven or eight (nonconsecutive) treatment days. Twelve subjects, six in each group, acknowledged completing some treatment periods later than the 8:00 am target. Eleven of these 12 subjects completed these treatment periods before 9:00 am. Mean expectation scores were similar and not statistically significantly different ($t = -.879$, $p = .389$), with 3.59 ± .22 (mean ± SE) for the 468 nm condition and 3.46 ± .25 for the 654 nm condition. Figure 2 compares SIGH-SAD scores of blue versus red groups at baseline and at each treatment week.

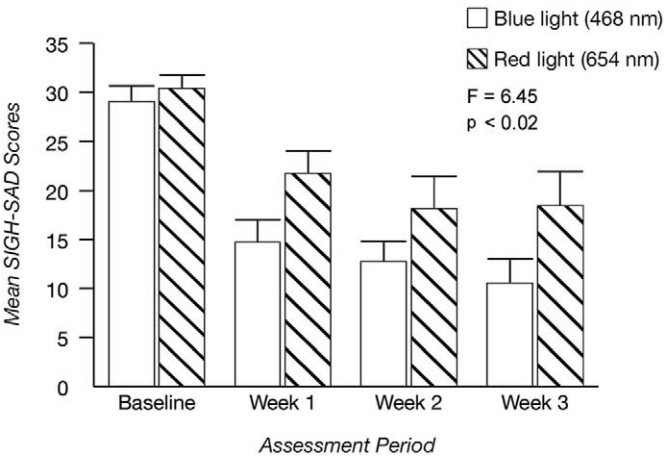

Figure 2. This figure shows a comparison between mean (+SEM) SIGH-SAD scores at each week in patients who were treated with the 468 nm blue light panel versus those treated with the 654 nm dim red light placebo device. While there was no difference between baseline scores across conditions, SIGH-SAD scores of patients treated with the blue LED light were significantly lower than SIGH-SAD scores of patients treated with the red LED light ($p < .02$). SIGH-SAD, Structured Interview Guide for the Hamilton Depression Rating Scale- Seasonal Affective Disorder version.

The main effect for light condition was statistically significant ($F = 6.45$, $p = .019$). The post-baseline mean SIGH-SAD scores for the 468 nm light was 7.3 points lower than that for the 654 nm light (95% confidence interval – 1.3, 13.2 points). Both the main effect for week and that for the week-by-condition interaction were small relative to that for condition and not statistically significant ($p = .419$ for week and $p = .597$ for week-by-condition). When remission of symptoms is defined as a reduction of SIGH-SAD score by ≥50% to a score of ≤8, 55% of patients using the 468 nm (blue) light treatment remitted while 31% remitted using the 654 nm (red) light panel, a difference that does not reach statistical significance with this sample size ($p = .41$ by Fisher's exact test). The standardized effect size, Cohen's *h*, was .48, a medium effect. Neither age nor the age-by-condition interaction was statistically significant. Adjusting for age produced a more significant effect for condition ($p = .009$); age of subjects using blue lights was 40 years (SE 3.53) versus 48.08 years (SE 3.60) for the red light group. Correlations of expectation scores to treatment responses were: for the total group, $r = -.28$; for the blue light group, $r = -.60$; and for the red light group, $r = -.11$.

As exploratory analyses, it was considered whether the effect of condition or the covariate baseline score differed by sex. The baseline-by-sex interaction reached statistical significance ($p = .031$). The effect of baseline, which was not significant in the primary analyses ($p = .495$), when averaged over sex, was significant in men ($p = .038$) and essentially unrelated to outcome in women. The condition-by-sex interaction was large, but did not reach statistical significance ($p = .070$). The estimated differences were 16.7 points for men and 4.4 points for women, both in favor of the 468 nm light compared to the 654 nm light. Remission rates in women, who comprise most of the patient groups, were 40% with red light and 56% with blue light, not a statistically significant difference.

Side effects were not formally assessed, although subjects were asked weekly if they were experiencing any adverse effects of light treatment. No subjects in either condition, including the two patients who were unable to complete the trial, reported any suspected side effects.

Discussion

In this trial, narrow-band LED technology was utilized to selectively test wavelength effects on SAD symptoms. Specifically, short-wavelength LEDs of 468 nm significantly outperformed the dim long-wavelength LED condition. Remission rates in patients using the 468 nm light panel were comparable to those typically reported in patients utilizing current standard bright white light treatment.

Regarding light safety, an independent hazard analysis following the national and international guidelines determined both red and blue LED light units to be well within the designated limits for photobiological safety (ICNIRP 1997; ACGIH 2003; ANSI/IESNA 1996). This assessment was done at the closest possible viewing distance of 0 cm even though patients were instructed to view the light panel at a distance of 50 cm. Potential long-term cumulative subthreshold damage by LED light units was not addressed in this hazard analysis, nor has it been assessed in light treatment for SAD with the standard white fluorescent light at 10,000 lux which emits wavelengths in the blue portion of the spectrum. For this reason, follow-up over time of patients using light therapy is recommended (Wesson and Levitt 1998). Future comparisons of narrow band blue light to narrow band green light may be useful for determining the comparative efficacy and safety of these interventions.

The spectral composition of the LED light source tested in this project may influence light therapy tolerance. The discomfort usually reported by some patients during light therapy appears to be due to glare, which is caused, in part, by intraocular light scatter that can reduce contrast and result in blurring of the retinal image (Ijspeert et al 1990). Wavelength may or may not affect glare (Boettner and Wolter 1962; Wooten and Geri 1987), but lower illuminances of light do serve to reduce intraocular light scatter. Therefore, identifying the most potent spectral characteristics for treatment of SAD may enable the future development of a device that would allow for the convenience of lower intensity and/or shorter duration light treatment and, consequently, further minimize side effects. The fact that subjects in this study did not complain of side effects from light therapy with the blue or red LED panels may have been due to factors of wavelength, reduced light intensity compared to standard white light, or lack of formal assessment. Formal side effect assessments of light at varying wavelengths and intensities with larger subject groups are clearly necessary. Though one might expect fewer side effects from a lower intensity light, as were both LED units used in this study, it is also possible that any morning light treatment which caused a phase advance in SAD sufferers might be associated with some side effects. It has been shown that LEDs at 470, 495 and 525 nm can elicit phase advances in healthy volunteers (Wright et al 2004). The present study did not examine circadian phase in SAD patients but such studies would be useful.

The recent availability of action spectra for acute light-induced melatonin suppression allowed for selective testing of spectra for the antidepressant benefits of light therapy (Brainard et al 2001b; Thapan et al 2001). Using selective wavelength comparisons in order to predict an action spectrum and photoreceptor physiology has been successful in previous studies of neuroendocrine systems and visual functions (Bronstein et al 1987). Although this study focused on a specific range of short wavelength light, further selected wavelength comparisons will be helpful in understanding the underlying phototransduction physiology that mediates the benefits of light therapy and to guide the development of optimized light therapy equipment.

As in the melatonin suppression trial performed prior to the clinical trial, the 468 nm LED condition outperformed the dim red light condition (Glickman et al 2003). Treatment response in the clinical trial, however, was not clearly predicted by melatonin suppression, as a significant decrease in SIGH-SAD scores was associated with dim red light treatment as well as with the blue light. Although mean group expectation scores were statistically equivalent, suggesting that placebo responses would be similar in each group, correlations of expectation to treatment responses were higher for the blue light group. This may suggest that blue light subjects derived more benefit from treatment than did red light subjects with comparable expectations.

In conclusion, narrow band blue LED light therapy shows promise as an effective treatment for SAD, outperforming dim red light. This study does not establish narrow band blue light as uniquely effective for SAD. Larger scale studies with other comparison conditions (e.g. narrow bandwidth blue, green and red lights of equal photon density compared to broad spectrum white light) need to be completed to determine the potency of narrow-band short wavelength light relative to current standard treatments.

We greatly appreciate the contributions of Henry and Kent Savage of Apollo Lighting Systems, Inc. in developing and providing the LED light units utilized in this study. Special thanks to Dr. David Sliney for performing the American Conference of Governmental Industrial Hygienists hazard analysis on light unit safety, and to Sharon Miller and Dr. Lawrence Kessler of the Food and Drug Administration for confirming the hazard analysis. A copy of that report is available; send requests to Dr. Brainard. Both Phyllis Fisher and Ruth Stevens were invaluable to subject recruitment. The frequent technical, graphics and editorial support of Aaron M.L. Steckelberg, Benjamin Warfield, Claudia Penrose, Jennifer Friedman, Laine Brainard and John Hanifin is greatly appreciated. Robert Levin (OSRAM Sylvania) and Robert Fucci were of great help with the photometric and radiometric characterizations of the LED panels. Lastly, two authors (GCB and GG) have a potential conflict of interest that has been appropriately reported to Thomas Jefferson University. They have a patent pending relating to short wavelength light for therapeutic purposes and were consequently blind to assigned conditions until the completion of the study.

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