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Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression

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ABSTRACT

Treatment of bipolar disorder often results in patients taking several drugs in an attempt to alleviate residual depressive symptoms, which can lead to an accumulation of side effects. New treatments for bipolar depression that do not increase the side effect burden are needed. One nonpharmacological treatment with few side effects, bright light therapy, has been shown to be an effective therapy for seasonal affective disorder, yet has not been extensively studied for other forms of depression. Forty-four adults with bipolar disorder, depressed phase were randomized to treatment with bright light therapy, low-density or high-density negative ion generator for 8 weeks. The primary measure of efficacy was the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS). Adverse events were assessed using the Young Mania Rating Scale (YMRS) and Systematic Assessment for Treatment Emergent effects (SAFTEE). All outcome variables were statistically analyzed using a mixed model repeated measure analysis of variance (ANOVA). The results showed no statistically significant differences between groups in any outcome measures at study end point; adverse events, including switches into hypomania, were rare. Further research is needed to determine the efficacy of bright light therapy in this population.

1. Introduction

Bipolar disorder is a common and often disabling illness, with the prevalence of bipolar disorder, type I, at approximately 1.6% (Kessler et al., 1994). There is general agreement that treatment of the depressed phase of illness remains the greatest challenge in the acute and long-term management of bipolar disorder (Calabrese, 2005). Several classes of medication are currently used for the treatment of bipolar depression, such as mood stabilizers, antidepressants and antipsychotic medications. These treatments are frequently only partially effective, leaving patients with residual depressive symptoms that can be problematic and are correlated with relapse (DePaulo, 2006). In refractory illness, it is common for medications to be added one after another, resulting in an accumulation of medications and side effects. There is clearly a need for adjunctive non-pharmacologic treatments that will complement medication regimens without adding to the side effect burden. Exposure to bright environmental light, or light therapy, has been proposed as one such treatment.

Several controlled trials of bright light therapy (BLT) have shown this to be an effective treatment for seasonal affective disorder, or SAD (Rosenthal et al., 1984; Lewy et al., 1998; Terman et al., 1998). Other studies show effectiveness of BLT for nonseasonal depression (Goel et al., 2005). More recent studies have shown BLT to be effective for depression in women with antepartum depression (Wirz-Justice et al., 2011), and in elderly adults with major depression (Lieverse et al., 2011) and a meta-analysis by Golden et al. (2005) concluded that light therapy was effective for nonseasonal depression. Only a few trials have looked specifically at patients with bipolar depression (Leibenluft et al., 1995; Sit et al., 2007). In a small study of light therapy in 17 patients with nonseasonal depression, patients with a bipolar history ($n=6$) showed greater improvement than those with unipolar depression (Deltito et al., 1991). Although bright light therapy has been considered safe, one potential side effect is development of hypomania. Other side effects, generally mild, have been reported in patients with SAD and include nausea, headache, eyestrain, irritability and fatigue (Labbate et al., 1994; Terman and Terman, 1999).

Of particular interest is the recent study of nine female patients with bipolar depression treated with adjunctive light therapy (Sit et al., 2007). The patients were treated with a 2-week lead-in exposure to dim red light followed by 7000 lx of white light either in the morning or at midday for durations starting at 15 min/day for 2 weeks and increased in 15-min increments every 2 weeks to 30 and then 45 min/day. The first four women received morning light therapy and then shifted to midday light because of the emergence of hypomania or mania in three of the four patients. Of the five subjects who received midday light, 2 responded fully, one responded partially, and

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two responded initially but did not maintain the response. The partial responder subsequently responded fully when light was moved to the morning.

The objectives of the current controlled exploratory trial were to determine whether light therapy is a safe and effective treatment for bipolar depression and, if so, to establish a protocol that would be used by clinicians in general practice. For comparison, a small study was included to evaluate possible benefit of high-density negative air ion treatment in bipolar depression.

2. Methods

2.1. Subjects

Forty-four subjects with bipolar depression who met all inclusion/exclusion criteria were enrolled and randomized in a balanced fashion into one of three treatment conditions: bright light therapy (BLT), low-density (LDNI), or high-density (HDNI) negative air ionization. Participants were volunteers, age 18 or older, signed written informed consent and were recruited from October 2007 to March 2009. All met DSM-IV criteria (American Psychiatric Association, 1994) for Bipolar I or II disorder, depressed phase, for at least 1 month before screening, during which there was no manic episode, as determined by the Mini International Neuropsychiatric Interview (Sheehan et al., 2006). Subjects were required to be on a stable dose of psychotropic medication for at least 2 weeks prior to enrollment, and to have a total score of 20 or more on the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS) (Williams et al., 2003) at screening and baseline visits, with a score of at least 10 on the typical items (HAM-D) of this scale and a Clinical Global Impression — Severity (CGI-S) (Guy, 1976) rating of 4 or higher.

Subjects were excluded from the study if they had a diagnosis of SAD according to DSM-IV criteria for seasonal pattern or a score of >12 on the Young Mania Rating Scale (YMRS) (Young et al., 1978) at either screening or baseline. The other main exclusion criteria were thyroid-stimulating hormone (TSH) levels with significant deviation from the normal range, another Axis I disorder as a principal diagnosis in the 6 months prior to screening, a decrease of 25% or more in SIGH-ADS score between screening and enrollment, a significant suicide risk, initiation of cognitive behavior therapy within 1 month of screening, a positive urine screen for illicit drugs or history of substance abuse or dependency in the 6 months prior to screening, enrollment in another research study within 2 weeks of screening, and if the subject was regarded, for any reason, by the principal investigator as being an unsuitable candidate for the protocol (medical condition, abnormal blood tests, and unlikely to comply). Subjects were also excluded if they had an ocular disorder or they were taking a photosensitizing agent, such as St. John's Wort, that made it potentially unsafe for them to undergo bright light therapy. Women who were pregnant, lactating or planning to become pregnant were also excluded.

2.2. Protocol

An outside investigator (M.T.) provided the negative ion generators coded so that all research staff remained blind to the intensity of ion flow for each device. Subjects were assigned to one of the three treatment groups using batched randomization in a 3:3:1 ratio. At each visit, a trained rater, who remained blind to allocated treatment, evaluated each subject using the SIGH-ADS, Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), CGI-S, Clinical Global Impression — Improvement (CGI-I; on visits 3 to 8), and YMRS. All subjects completed the Seasonal Pattern Assessment Questionnaire (SPAQ) (Hardin et al., 1991) at screening. A self-administered Expectancy Rating Questionnaire (ERQ) measuring expected magnitude of response was given at baseline. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al., 1993) and the self-rating version of the Systematic Assessment for Treatment Emergent Effects (SAFTEE) (National Institute of Mental Health, 1986) were completed at each study visit from baseline to week 8.

During the study, research psychiatrists and staff who were not blind to treatment assignment were responsible for treatment management and other clinical evaluations. All subjects were required to be on a stable dose of their psychotropic medication for at least 2 weeks prior to enrollment. Bipolar I patients were required to be on a mood stabilizer or combination of mood stabilizers judged by the investigator to be sufficient. If either lithium or valproic acid was used alone, minimum levels of 0.4 mEq/L and 50 mEq/L, respectively, were required. Subjects with a satisfactory medication regimen at screening were eligible for randomization the same day if all other inclusion and no exclusion criteria were met.

Subjects were not prohibited from taking any medications during the study except photosensitizing agents such as St. John's Wort. However, once enrolled, no change in the dosage of any psychotropic medication was allowed. Benzodiazepines were allowed at up to 2 mg of lorazepam-equivalents per day and zolpidem (5 to 10 mg) or zaleplon (5 to 10 mg) were permitted for insomnia as long as none of these medications were taken more than 3 days per week or within 12 h of any study assessment.

The study was divided into three phases: screening and stabilization (0 to 31 days), treatment (8 weeks) and follow-up (8 weeks). The treatment regimen was carefully explained to each subject. Treatment duration began at 7.5 min upon rising in the morning. After 3 days of treatment, there was a telephone visit to establish whether treatment duration could be safely increased to 15 min/day. If there were any signs of hypomania or other untoward side effects, the subject was either kept at 7.5 min/day for the rest of the week or treatment was skipped until the hypomania subsided, and then reinstated at 7.5 min each morning. If subjects could not tolerate 7.5 min light exposure, they were encouraged to try 15 minutes of treatment at midday. Subjects were instructed to call in at any time if they had any adverse symptoms.

After randomization, subjects were seen at weeks 1, 2, 3, 4, 6 and 8. Telephone calls were made to the patient 3 days after each office visit, when the clinician would decide to lower, maintain or increase the treatment duration (as described above). Each week, the duration could be increased by a maximum of 15 min, in 7.5-min increments, to a maximum exposure of 45 min/day. Mid-week corrections in treatment duration were allowed until week 4; thereafter, the duration remained fixed unless problems occurred. During the follow-up period (weeks 8 to 16), subjects were treated in an open fashion, medications were adjusted if necessary and referral to appropriate outside clinicians for continued care was provided.

In the informed consent process, in order to balance expectations, participants were told that both BLT and negative ion therapy have been found to be effective in treating some forms of depression, although this had not been well studied in bipolar depression. The study design was presented as a comparison of light therapy and negative ion therapy and that differing intensities of negative ions would be compared.

2.3. Treatment devices and procedures

2.3.1. Light boxes

Light therapy was administered by means of the Day-Light *Model 930* (Uplift Technologies, Inc., Dartmouth, NS, Canada). This device measures $33.7 \times 40.6 \times 7.6$ cm, with lens material of high-impact polycarbonate, 99.3% UV filter, three 36-watt fluorescent bulbs of 4000-Kelvin color temperature, with height-adjustable legs and two light intensity settings of 10,000 and 7000 lx at 12 in. (30.5 cm). Subjects were instructed to place the box on a desk or tabletop at an angle of 15°, to adjust the height so the center of the box was at eye level, and to use the 7000 lx setting with their face fully exposed without staring into the light.

2.3.2. Negative ion generators

Ion treatment was administered using the FreshAIR negative ion generator modified with a grounded wrist strap (SphereOne, Inc., Silver Plume, Colorado, USA) to maximize ion flow toward the body. The flow rate for the low-density device was 1.7×10^{11} ions/s and 4.5×10^{14} ions/s for the high-density device. Patients were instructed to place the device on a tabletop that did not hold any other electrical devices. They were to position the negative ion generator with the ion emitter wand pointing in their direction and to sit 3 ft (91.4 cm) from the unit. Additional instructions for subject safety, proper device use and maintenance were provided. A dim neon indicator light on the unit illuminated when the device was on, but the light indicating momentary ion flow rate was disabled to maintain the “blind” condition.

2.4. Outcome measures and statistical methods

Because this is the first controlled trial of BLT for the treatment of bipolar depression and there are few data about the effect size of the two interventions, the sample size could not be estimated on the basis of statistical considerations. However, sample sizes of 18 and 20 for the Light and the Low control group, respectively, were considered adequate for an exploratory study of this treatment modality. Responders were defined as those subjects with a decrease in SIGH-ADS score of 50% or more from baseline; remission was defined as a score of 8 or less on the SIGH-ADS at end point.

The primary and secondary outcome measures were assessed using a 3 group × 7 time-period mixed model repeated measure analysis of variance (ANOVA). Basic descriptive statistics including the mean, standard deviation, variance and range were calculated for primary, secondary and demographic variables and vital signs.

All subjects were evaluated for seasonality using the SPAQ, a self-rating scale that provides a Global Seasonality Score (GSS) for seasonal variations in sleep, social activity, mood, weight, appetite and energy level. A GSS score of 11 or higher (range, 0 to 24) indicates clinically significant seasonal variation in these symptoms. To assess the role of seasonality in response to BLT, statistical analysis of the MADRS, with GSS as a covariate, was performed. The GSS covariate was analyzed as a regression covariate and as an above and below the median grouping factor. In addition, for the Light group, MADRS scores for subjects enrolled in the winter were compared with those enrolled during other seasons.

3. Results

Ninety-two subjects were screened, of which 44, with a DSM-IV diagnosis of Bipolar Disorder, Type I or II in the depressed phase of illness, were enrolled. There were no statistically significant differences between groups at baseline for demographics, vital signs or the primary and secondary outcome variables. Table 1 lists demographics for subjects in the Light and Low groups. Twenty-three subjects completed the study (10 Light, 11 Low, 2 High). As there were very few