

Controlled trial of bright light and negative air ions for chronic depression

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ABSTRACT

Background. This randomized controlled trial investigates the efficacy of two non-pharmacologic treatments, bright light and high-density negative air ions for non-seasonal chronic depression. Both methods have shown clinical success for seasonal affective disorder (SAD).

Method. Patients were 24 (75%) women and 8 (25%) men, ages 22–65 years (mean age \pm s.d., 43.7 ± 12.4 years), with Major Depressive Disorder, Single Episode (DSM-IV code, 296.2), Chronic (episode duration ≥ 2 years). Patients were entered throughout the year and randomly assigned to exposure to bright light (10 000 lux, $n=10$), or high-density (4.5×10^{14} ions/s flow rate, $n=12$) or low-density (1.7×10^{11} ions/s, $n=10$, placebo control) negative air ions. Home treatment sessions occurred for 1 h upon awakening for 5 weeks. Blinded raters assessed symptom severity weekly with the Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder (SIGH-SAD) version. Evening saliva samples were obtained before and after treatment for ascertainment of circadian melatonin rhythm phase.

Results. SIGH-SAD score improvement was 53.7% for bright light and 51.1% for high-density ions v. 17.0% for low-density ions. Remission rates were 50%, 50% and 0% respectively. The presence or severity of atypical symptoms did not predict response to either treatment modality, nor were phase advances to light associated with positive response.

Conclusions. Both bright light and negative air ions are effective for treatment of chronic depression. Remission rates are similar to those for SAD, but without a seasonal dependency or apparent mediation by circadian rhythm phase shifts. Combination treatment with antidepressant drugs may further enhance clinical response.

INTRODUCTION

Bright light and high-density negative air ion exposure both have been used successfully to treat the winter depressive episode of seasonal affective disorder (SAD) (Terman & Terman, 1995; Terman *et al.* 1998*b*). These non-pharmaceutical interventions have fewer side-effects and contraindications than antidepressant drugs.

The treatments may also be useful for patients with non-seasonal major depression who do not continue or cannot tolerate antidepressants, fail to maintain positive response, or are drug non-responders. Early studies found modest improvement after 1 week of light treatment (Mackert *et al.* 1991; Volz *et al.* 1991; Kripke *et al.* 1992; Yamada *et al.* 1995; Baumgartner *et al.* 1996). In an overview, Kripke (1998) concluded that bright-light therapy produces a net advantage of 12–35% relative to dim-light placebos, and more rapid improvement than with drugs. A recent Cochrane meta-analysis

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confirmed this therapeutic benefit (Tuunainen *et al.* 2004) and an American Psychiatric Association work group concluded that efficacy appears equivalent to that of antidepressant drugs (Golden *et al.* 2005).

A basic question remains, however: Does the improvement depend on seasonal modulation of depression severity even in the absence of seasonal recurrence? Most studies have excluded subjects whose depressions met DSM-III, -III-R or -IV criteria for the seasonal pattern specifier. However, the specifier is based entirely on the timing of discrete winter major depressive episodes, and does not take into account depressions that, while present across the seasons, show winter exacerbation. The well-established seasonality scale of Rosenthal and colleagues (1987) has not been administered to putative non-seasonal patients except in one study (Neumeister *et al.* 1996) that found the global seasonality score (GSS) overlapped the range of subsyndromal SAD (GSS ≥ 11 on a scale of 0–24) (Kasper *et al.* 1989). In a large population sample, White & Terman (2004) found that 85% of subjects with GSS ≥ 11 indicated major depressive episodes in winter. Therefore, it is likely that non-seasonal studies have included subjects with winter worsening, and it remains unknown whether the absence of seasonality negates the response to light.

The circadian timing system has been implicated in the antidepressant action of bright-light therapy for SAD. Morning light is superior to evening light (Lewy *et al.* 1998; Terman *et al.* 1998*b*) and may exert its therapeutic effect by advancing the phase of circadian rhythms (Lewy *et al.* 1987; Sack *et al.* 1990). Indeed, the size of phase advances of the melatonin rhythm correlates positively with clinical response (Terman *et al.* 2001). Morning light also advances rhythms in patients with non-seasonal depression (Rao *et al.* 1992; Thalén *et al.* 1995*b*, 1997; Yamada *et al.* 1995), although no significant correlation with treatment response has been reported.

Negative air ions in the ambient circulation – concentration tends to be higher in summer than winter and in humid than dry environments – has long been contended to have mood-elevating effects (Soyka, 1977), although until recently there have been no

placebo-controlled studies (Terman & Terman, 1995; Terman *et al.* 1998*b*). In response to negative ion exposure, subjects have reported reduced irritability, depressed mood and tension, and increased calmness and relaxation (Buckalew & Rizzuto, 1982; Baron *et al.* 1985). By contrast, a higher balance of positive air ions – as is found in artificially heated and air-conditioned home and work environments – has been associated with increased irritability, depressed mood and tension (Tom *et al.* 1981).

A pure double-blind placebo for bright light is impossible to achieve, since patients see the stimulus. To address this problem, Eastman and colleagues (1998) devised a deactivated negative ion generator as a single-blind placebo control. Importantly, the daily behavioral commitment to treatment sessions was equated. Patients with SAD viewed the intervention as credible, with expectations similar to those for bright-light therapy. We first tested active negative air ions as a treatment for SAD in controlled studies of daily exposure to high or low densities (Terman & Terman, 1995; Terman *et al.* 1998*b*). After several weeks, the remission rate to high-density ions was similar to that for light therapy, while low-density ions produced minimal improvement. Since differences in ion density are imperceptible (Yates *et al.* 1986), with no known sensory organ for this physical stimulus, the studies achieved a true double blind. Thus far, negative air ionization has not been tested for non-seasonal depression. Furthermore, its antidepressant mechanism of action – which might also involve a circadian effect – has not been explored.

In the present trial, we tested the efficacy of light and negative air ion treatments in outpatients with chronic major depression of at least 2 years' duration, who reported no seasonal modulation (GSS ≤ 6). We hypothesized that – like for SAD – morning exposure to light or high-density ions would produce similar reductions in depressive symptoms on the Hamilton scale along with a scale for atypical neurovegetative symptoms, and that both treatments would yield responses surpassing that of low-density ions. Additionally, we examined whether the response to light or ions is related to the circadian rhythm of melatonin production, and hypothesized that only light would produce phase advances.

METHOD

Subjects

Patients were 32 volunteers, 24 (75%) women and 8 (25%) men, ages 22–65 years (mean \pm s.d., 43.7 ± 12.4 years), all with Major Depressive Disorder, Single Episode (DSM-IV code, 296.2), Chronic (episode duration ≥ 2 years). Diagnoses were based on the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID; First *et al.* 1995). Twenty-one patients (66%) met criteria for DSM-IV Atypical Features, as assessed with the Diagnostic Interview for Atypical Depression (Terman *et al.* 1998a) and eight patients (25%) met criteria for Melancholic Features, as assessed with the SCID. The DSM-IV Seasonal Pattern specifier was exclusionary, as was GSS > 6 . Additional exclusions were the presence of another Axis I disorder, recent history of a suicide attempt, habitual waking after 09:00 hours or bedtime later than 01:00 hours and past treatment with light or ions.

Depression severity was assessed using the combined 21-item Hamilton and 8-item atypical symptom scales of the *Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder Version* (SIGH-SAD; Williams *et al.* 1994), which although originally designed for SAD studies is equally applicable for assessment of non-seasonal depression with atypical features (as in the present study). The Hamilton and atypical symptom subscales of the SIGH-SAD can be analyzed separately or in combination. The minimum SIGH-SAD score for entry was 20, with Hamilton score ≥ 10 and atypical symptom score ≥ 5 . In patients with SAD, both subscales have been useful for identifying superior response to light and high-density ions relative to the low-density ion control (Terman & Terman, 1995; Terman *et al.* 1998b).

Psychotropic drugs [other than allowable, pre-established use of selective serotonin reuptake inhibitors (SSRIs), an option only exercised by two patients], recreational drugs or alcohol were not allowed. Patients were medically healthy as determined by a physical examination with standard blood tests including a thyroid panel. All patients signed informed consent after the procedures had been fully explained. The study was conducted concurrently

at New York State Psychiatric Institute (NYSPI) and the Department of Psychology, Wesleyan University, with separate institutional review board approval.

Procedure

Patients were assigned to one of three treatment conditions: bright light (10 000 lux, $n=10$), high-density negative air ionization (flow rate 4.5×10^{14} ions/s, $n=12$) or low-density ionization (1.7×10^{11} ions/s, $n=10$). Successive assignments were drawn from a random-number table, with compensatory catch-up for cells with low entry after every 10 patients. High- v. low-density ions formed a double-blind comparison, while light v. high- or low-density ions formed single-blind comparisons. Patients were entered throughout the year and treatment for all groups occurred nearly equally in the spring/summer [April–September ($n=15$): lights ($n=4$), high-density ions ($n=5$), low-density ions ($n=6$)] and autumn/winter [October–March ($n=17$): lights ($n=6$), high-density ions ($n=7$), low-density ions ($n=4$)]. Recruitment also was nearly equal at both sites (NYSPI, $n=18$; Wesleyan, $n=14$). Treatment was taken at home, daily for 5 weeks, for 1 h within 10 min of waking. Patients maintained a consistent, habitual, individualized sleep–wake schedule 2 weeks before and during the protocol, monitored by sleep log review. Treatment compliance was monitored by daily messages to an answering machine with time stamp. At the end of the 5-week trial, patients were informed of their treatment condition.

Before randomization, patients made expectation ratings for treatment response to both light and ions on a scale of 1–5 (1, no improvement; 2, minor improvement; 3, moderate improvement; 4, major improvement; 5, full improvement). Trained raters blinded to the treatment assessed response weekly using the SIGH-SAD, our primary outcome measure; response with remission was defined as a pre- to post-treatment reduction in SIGH-SAD score to ≤ 8 (Terman *et al.* 1998b). Given the minimum entry score of 20, all responders showed $\geq 60\%$ improvement. All 32 patients completed the full 5-week course of treatment. One additional patient, excluded from analysis, dropped out because of lack of response after 2 weeks on low-density ions.

Apparatus

Light treatment used SPX-30 triphosphor fluorescent lamps at 3000 K color temperature, encased in a metal box (27.9 × 58.5 cm) with a translucent plastic diffusing screen (Uplift Technologies Inc., Dartmouth, Nova Scotia, Canada). The box was mounted on a height-adjustable table-top stand and was tilted on a downward angle of 30° toward the head. The center of the screen was placed ~32 cm from the eyes and provided illuminance of ~10 000 lux. Direction of gaze was toward the illuminated area beneath the light source and patients were instructed not to look directly at the screen.

The negative ion generators produced different flow rates but were identical in appearance (4.5×10^{14} ions/s v. 1.7×10^{11} ions/s; SphereOne Inc., Silver Plume, CO, USA). Ionization at the lower level (termed a 'dribble' by the manufacturer) rapidly dissipates, barely affecting concentration in the ambient air circulation. While the lower, control level was the same as in our previous studies of patients with SAD (Terman & Terman, 1995; Terman *et al.* 1998b), the higher level was increased by one order of magnitude (10^{14} v. 10^{13} ions/s) in an attempt to further potentiate the dose. The ionizer was placed at least 92 cm from walls and away from electronic devices, grounded surfaces and ventilation ducts, which attract and neutralize the ions. Windows and doors remained closed during treatment sessions to increase ambient concentration. Patients sat ~32 cm from the ionizer and wore a grounded wrist strap to maximize ion flow toward the body.

After treatment assignment, patients received a demonstration of the respective treatment apparatus and instructions regarding permissible activities during exposure. Across all conditions, subjects were instructed to read, write, eat breakfast, listen to music, or engage in other sedentary activities in close proximity to the treatment apparatus. Subjects were required to remain seated and awake, with their eyes open throughout the treatment hour.

Salivary melatonin

Patients collected nine saliva samples at 30-min intervals under dim-light conditions at home on two evenings, before their habitual bedtimes at

baseline and after 5 weeks of treatment. Dinner was completed at least 30 min before sampling, when patients put on light-attenuating fit-overs with side shields with 4% transmission (Model U23, Noir Medical Technologies, South Lyon, MI, USA) until sampling was completed. No food was permitted and water was permitted only within 5 min after each sample. Saliva (1.0–3.0 ml) was deposited into Salivette tubes (Sarstedt, Nümbrecht, Germany) using absorbent polyester swabs placed in the mouth for 5 min. The refrigerated samples were returned in a cold bag and were stored at -20°C pending laboratory assay.

The dim-light melatonin onset (DLMO), a reliable marker of circadian rhythm phase (Lewy & Sack, 1989), was defined as the first interpolated point at 3.0 pg/ml on the rising curve of melatonin concentration. A double-antibody direct radioimmunoassay was used (Bühlmann Laboratories AG, Allschwil, Switzerland). Samples of 200 μl were run in duplicate. The intra- and inter-assay coefficients of variation were $<5\%$ and $<9\%$ at quality control levels of 1.6 pg/ml and 16 pg/ml respectively. Absolute recovery was $>95\%$, with a lowest detectable limit of 0.5 pg/ml. All samples for a given patient were analyzed in the same run.

Statistics

Since this was the first investigation of light and ion treatment for chronic depression, with no preliminary data to estimate effect size, the recruitment goal was set at approximately 30 subjects without an *a priori* power analysis in order to make an initial determination of prospects for these interventions. Repeated-measures analysis of variance (ANOVA), with baseline score as a covariate, assessed SIGH-SAD score changes across all treatment weeks. Additionally, groups were contrasted in terms of the mean \pm s.d. slope of the linear regressions on time. Two-tailed *t* tests were used for within-group paired comparisons and between-group unpaired comparisons, using Bonferroni correction for *post-hoc* comparisons. Categorical comparisons utilized the χ^2 test. The correlation between continuous measures was specified with Pearson's *r*. For all tests, an α -level of 0.05 was set as the threshold for significant differences. For *post-hoc* analyses, the α -level was corrected

Table 1. Baseline and end-point measures of depression severity and circadian rhythm and sleep phase (mean \pm s.d.)

Sample size ...	Treatment group		
	Bright light 10	High-density negative air ionization 12	Low-density negative air ionization 10
SIGH-SAD total score (29 items)			
Baseline	23.9 \pm 3.3	26.6 \pm 5.2	26.0 \pm 3.1
Week 5	11.4 \pm 8.6	13.1 \pm 9.3	22.2 \pm 7.7
Change, %	53.7 \pm 34.3*†	51.1 \pm 34.4*†	16.4 \pm 22.1*
Hamilton subscale (21 items)			
Baseline	15.5 \pm 3.0	17.9 \pm 3.5	17.3 \pm 2.8
Week 5	7.8 \pm 6.8	8.3 \pm 6.5	13.2 \pm 6.0
Change, %	54.0 \pm 33.3*†	54.4 \pm 33.8*†	25.8 \pm 25.0*
Atypical symptom subscale (8 items)			
Baseline	8.4 \pm 3.3	8.7 \pm 4.1	8.7 \pm 2.4
Week 5	3.6 \pm 3.2	4.8 \pm 3.5	9.0 \pm 3.7
Change, %	55.2 \pm 45.6*†	38.7 \pm 46.6*†	-3.5 \pm 36.7
Melatonin onset (h)			
Baseline	20.7 \pm 1.5	20.2 \pm 0.8	21.0 \pm 1.8
Week 5	20.2 \pm 1.5	20.3 \pm 1.3	21.5 \pm 1.6
Change	0.6 \pm 1.0†	-0.2 \pm 1.4	-0.9 \pm 0.9*
Sleep onset (h)			
Baseline	23.3 \pm 1.1	23.3 \pm 1.0	24.0 \pm 1.3
Week 5	23.2 \pm 1.0	23.3 \pm 0.8	23.9 \pm 1.3
Change	0.1 \pm 0.4	-0.0 \pm 0.6	0.0 \pm 0.6
Sleep midpoint (h)			
Baseline	2.9 \pm 1.0	3.1 \pm 0.7	3.7 \pm 1.4
Week 5	2.7 \pm 1.0	2.9 \pm 0.6	3.6 \pm 1.4
Change	0.2 \pm 0.3*	0.2 \pm 0.4	0.1 \pm 0.5
Sleep offset (h)			
Baseline	6.5 \pm 1.1	6.8 \pm 0.6	7.4 \pm 1.6
Week 5	6.2 \pm 1.1	6.5 \pm 0.7	7.2 \pm 1.6
Change	0.3 \pm 0.3*	0.4 \pm 0.3*	0.2 \pm 0.5

* $p \leq 0.05$, two-tailed *post-hoc t* test following significant three-group ANOVA, comparing baseline and week 5.

† Significantly different from the low-density ion group, $p \leq 0.02$ (ANOVA with *post-hoc* comparisons).

and data are presented with corrected p values. The effect size of means and proportions was specified with Cohen's d and h respectively.

RESULTS

Treatment response

The severity of depression at baseline was moderate (mean \pm s.d. SIGH-SAD score, 25.6 \pm 4.1) and was closely equivalent for the three groups (Table 1). Repeated-measures ANOVA (with no missing data), including baseline score as a covariate, revealed a significant group \times time interaction ($F = 2.34$, $df = 8, 50$, $p = 0.03$). As illustrated in Fig. 1, all three groups showed response, with the largest change occurring during week 1 (pooled data: 28.1% \pm 24.0% improvement or 7.4 \pm 6.5 points on the

depression scale). Continued progress, on average, increased monotonically for the bright-light group, while patients given high-density ions showed an intermediate decline, close to placebo rates, in weeks 3–4, followed by major improvement in week 5. At the end-point evaluation, both active treatments surpassed low-density ions in efficacy (two-tailed *post-hoc t* tests: light, $p < 0.02$; high-density ions, $p < 0.04$).

The consistency of improvement under high-density ions relative to the low-density control – masked in Fig. 1 by the variability of weekly means – is underscored by the linear regressions of depression scores on time, as shown in Fig. 2. In this analysis, the essential measure of improvement is the slope, m , with increasing negative slope indicating greater response. The mean slopes for the two active treatments are

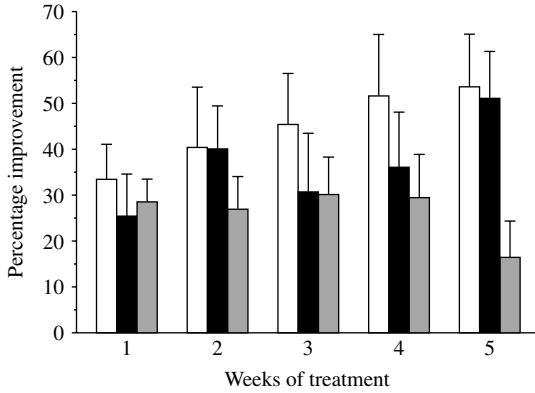


FIG. 1. Percentage improvement (\pm S.E.M.) on the *Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder Version* (SIGH-SAD) over 5 weeks of treatment with bright light (\square , $n=10$); high-density negative air ions (\blacksquare , $n=12$); or low-density negative air ions (\square , $n=10$).

nearly identical, with large effect sizes relative to low-density ions. Individual patients' slopes vary widely under all treatment conditions, reflecting the mix of responders and non-responders. Under low-density ions, the preponderant slopes were near zero (no improvement in five patients) or moderately negative (partial improvement in four patients), with one case of a large positive slope reflecting symptom exacerbation. By contrast, large negative slopes were found only under bright-light and high-density ion conditions.

Over the 5 weeks of treatment, the low-density ion group improved by only 3.8 ± 5.3 points in comparison to 12.5 ± 7.9 points for light and 13.0 ± 10.0 points for high-density ions. This result was mirrored in remission rates [SIGH-SAD score ≤ 8 : light, 50.0% (5/10 patients); high-density ions, 50.0% (6/12 patients)], which showed a large effect size relative to low-density ions [0% (0/10 patients), $h=1.57$]. SIGH-SAD score improvement was not significantly correlated with baseline severity (lights: $r=-0.33$, $n=10$, $p>0.1$; high-density ions: $r=-0.05$, $n=12$, $p>0.1$). Separately, the 21-item Hamilton and 8-item atypical symptom subscales showed the same pattern of improvement and significant group differentiation as the total SIGH-SAD score (Table 1).

In comparisons of treatment results for the autumn/winter v. spring/summer months, there was no significant seasonal variation in either percentage improvement ($46.69\% \pm 36.41\%$ v.

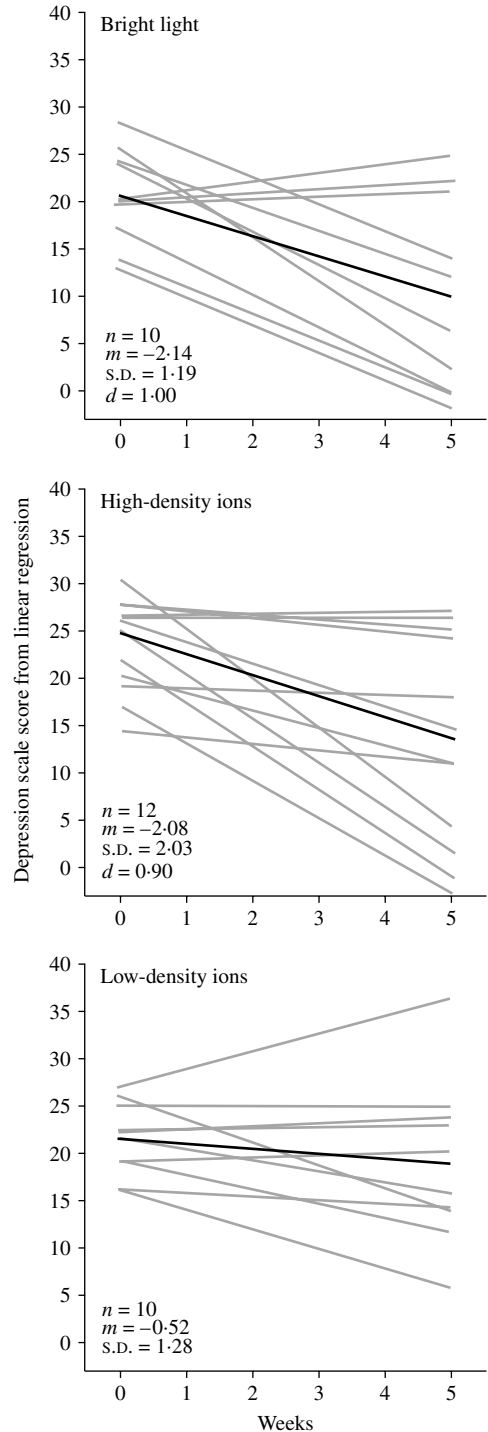


FIG. 2. Linear regressions of SIGH-SAD score by week. Week 0, baseline. Gray lines, individual patients; black lines, group means. m , Mean slope for each group; d , effect size relative to low-density ions.

34.63% \pm 32.17%; $F=0.24$, $df=1$, 26 , $p>0.1$) or remission rate (8/17 v. 3/15; $\chi^2=7.43$, $df=1$, $p>0.1$). Rating scale scores for patients with atypical v. melancholic features did not differ at baseline (25.48 \pm 4.30 v. 25.75 \pm 4.71; $F=0.02$, $df=1$, 27 , $p>0.1$) or treatment end-point (16.48 \pm 9.30 v. 10.75 \pm 10.65; $F=2.03$, $df=1$, 27 , $p>0.1$). Furthermore, atypical balance (atypical score/total SIGH-SAD score \times 100) (Terman *et al.* 1996) did not significantly predict treatment response (light: $r=0.49$, $n=10$, $p>0.1$; high-density ions: $r=-0.01$, $n=12$, $p>0.1$). Expectation ratings were slightly but significantly higher for light than for negative ions (3.13 \pm 0.83 v. 2.78 \pm 0.98; $F=6.37$, $df=1$, 29 , $p=0.02$), with similar ratings across the three groups. However, expectations did not significantly predict treatment response (light: $r=0.28$, $n=10$, $p>0.1$; high-density ions: $r=0.35$, $n=12$, $p>0.1$) and did not vary between patients with atypical v. melancholic features (2.83 \pm 0.74 v. 3.13 \pm 1.22; $F=0.76$, $df=1$, 27 , $p>0.1$) or responders v. non-responders (2.81 \pm 0.89 v. 3.23 \pm 0.91; $F=1.90$, $df=1$, 30 , $p>0.1$).

The two patients who continued SSRIs during the study were randomized to the bright-light group. Both responded, without clinically noticeable difference from those using light alone. Of 22 patients in the active treatment groups, only three had no medication history. Of seven non-responders to either treatment, six had histories of non-response to various antidepressant drugs, while eight of the nine responders had experienced partial response to drugs ($\chi^2=9.58$, $df=1$, $p=0.004$).

Circadian phase and sleep

Baseline melatonin onset was similar for all three groups and spanned a wide range (18:16 hours to 23:23 hours, Table 1), similar to that seen in patients with SAD (Terman *et al.* 2001) as well as non-depressed subjects. Morning-light exposure produced a non-significant phase advance ($p>0.1$) that, however, was similar in magnitude to the significant advances found with a larger sample size in patients with SAD (Terman *et al.* 2001). The morning-light phase advance differed significantly from the delay ($p=0.04$) produced by low-density ions (Table 1), while the average phase shift with high-density ions was negligible and did not differ from

that with either light or low-density ions. For light, later baseline DLMOs predicted the largest phase advances ($r=-0.71$, $n=9$, $p=0.03$), but also poorest treatment response ($r=-0.89$, $n=10$, $p=0.001$). Specifically, the three patients with the largest phase advances (1.59 \pm 0.41 h) were all non-responders. For high-density ions, baseline DLMOs did not predict phase changes ($r=-0.14$, $n=9$, $p>0.1$) or treatment response ($r=0.27$, $n=11$, $p>0.1$). Overall, phase changes were not significantly correlated with treatment response for light ($r=-0.37$, $n=9$, $p>0.1$) or ions ($r=-0.09$, $n=9$, $p>0.1$).

Although baseline sleep onset and offset appeared generally later in the low-density ion group (Table 1), differences were not statistically significant. Baseline sleep and melatonin onsets were significantly correlated in both the light ($r=0.84$, $n=10$, $p=0.002$) and low-density ion ($r=0.90$, $n=9$, $p=0.001$) groups, while the high-density ion group showed a moderate but non-significant correlation ($r=0.47$, $n=11$, $p>0.1$). Sleep onset did not change significantly after treatment in any of the groups; thus, the phase-angle difference between melatonin onset and sleep also did not change. Post-treatment correlations between melatonin onset and sleep onset mirrored the pattern at baseline (light: $r=0.89$, $n=9$, $p=0.001$; high-density ions: $r=0.14$, $n=9$, $p>0.1$; low-density ions: $r=0.92$, $n=7$, $p=0.003$). Overall, responders to both light and high-density ions had significantly earlier sleep onsets than non-responders (light, $p=0.003$; ions, $p=0.03$).

Sleep offset advanced significantly following both light and high-density ion treatment (Table 1), though this was not correlated with treatment response (light: $r=-0.47$, $n=10$, $p>0.1$; high-density ions: $r=0.11$, $n=12$, $p>0.1$). The sleep mid-point, a measure of overall sleep phase position, showed a post-treatment phase advance (corresponding with the melatonin shift) only in the light group. Responders to light showed a significantly earlier sleep mid-point than non-responders ($p=0.04$), but this did not reflect a change from baseline.

DISCUSSION

Morning presentation of bright light or high-density negative ions each produced clinical

remission in 50% of chronically depressed patients within 5 weeks of treatment, while there were no remissions under low-density ions. The response rates to the active treatments are similar to those seen for SAD (Terman *et al.* 1998*b*), although derived from smaller sample sizes. The absence of a seasonal treatment dependency in a group strictly screened for history of seasonal recurrence or exacerbation indicates that these two non-pharmacologic modalities are effective irrespective of their time of administration across the year.

Earlier comparison studies of patients with and without SAD found the latter group less responsive to light therapy (Yerevanian *et al.* 1986; Stewart *et al.* 1990; Thalén *et al.* 1995*a*, 1997). It is possible that treatment parameters such as longer daily exposure duration and higher intensity, and longer course of treatment – as we used here – are needed to enhance light response in non-seasonal depression. Similarly, although the active ion dose was one order of magnitude higher in this study than in our earlier studies of SAD (10^{14} v. 10^{13} ions/s), it took longer to achieve significant improvement relative to low-density ions. Perhaps marked environmental changes in ion concentrations in winter (Soyka, 1977) render SAD patients more sensitive to negative ion exposure than patients with non-seasonal depression, thus producing faster improvement. On the other hand, the 5-week trial duration may have served to slow the rate of improvement under light and high-density ions alike by discouraging high expectations for rapid response; indeed, our earlier, shorter trials with SAD patients produced group differences within 1–2 weeks. Other studies of light therapy for SAD have also pointed to this trial duration factor (Eastman *et al.* 1998; Avery *et al.* 2001; Levitt & Levitan, 2003).

We found that the baseline severity of atypical neurovegetative symptoms, as assessed on the SIGH-SAD subscale, was markedly lower for chronic depression than in our study of SAD (Terman *et al.* 1998*b*) (8.59 ± 3.28 v. 12.84 ± 3.70 , $p < 0.001$). Apart from severity, the prevalence of DSM-IV atypical features has been shown to be similar in seasonal and non-seasonal patient samples (Terman *et al.* 2003) and, under both light and ion treatments, both groups show parallel improvement in atypical

symptom and Hamilton depression scores. Atypical neurovegetative symptoms are hallmarks of SAD (Rosenthal *et al.* 1984) and predict response to light therapy (Nagayama *et al.* 1991; Terman *et al.* 1996), but the presence of such symptoms did not presage success for our patients with chronic depression.

Our study corroborates others that found that circadian rhythm phase advances to morning light fail to show a correlation with treatment response in depressed patients without SAD (Rao *et al.* 1992; Thalén *et al.* 1995*a*, 1997; Yamada *et al.* 1995; Gordijn *et al.* 1998). Our relatively small sample size and large phase change variability may have hindered detection of a significant phase advance even though the mean shift was similar to that established for SAD (Terman *et al.* 2001). Furthermore, the phase delay observed under low-density ions provides a significant contrast with the response to light, although the origin of the phase delay remains unclear. It is important to note that melatonin onset did not shift under effective high-density negative ion treatment. Thus, circadian phase advances appear neither necessary nor sufficient for an antidepressant response in chronic depression.

The reduced efficacy of light therapy in patients with delayed baseline melatonin onset phase, who also showed the greatest post-treatment phase advances, contrasts with our findings for SAD (Terman *et al.* 2001), which showed no dependency of baseline phase position on treatment response. Apart from their phase delay, the explanation may lie in patients' histories of non-response to antidepressant drugs. As a group, such patients showed less improvement with light or high-density ions than those who had experienced partial drug response in the past. An implication is that treatment resistance applies to drugs and our non-pharmaceutical alternatives alike. A given patient, however, may respond differentially to drugs, light and negative ions. For example, of seven patients in our study who tried the alternate active treatment after completing the protocol, three showed better response to light, one responded equally to light and ions, and three were non-responders to both. Such variations correspond to an unpublished dataset for SAD from patients in our earlier study (Terman *et al.* 1998*b*), in which 42% (19/45 patients) showed

better response to light while 11% (5/45 patients) showed better response to ions.

To date, the mood-enhancing mechanism of negative air ions remains unknown, although preliminary work in animals and humans suggests effects on both central and peripheral serotonergic activity (Charry, 1987), as well as neural responsiveness to serotonin administration (Dowdall & de Montigny, 1985). Similarly, serotonergic activation has been put forth as a mediator of response to light therapy in addition to catecholamine activation (reviewed in Neumeister, 2004). The neurochemical substrates of light and ion therapy may overlap that of antidepressant drugs.

Our patients showed slightly higher expectations for bright light than negative ions, which differed by <0.5 of a point on a scale of 1–5, both within the range of predicted moderate improvement. A possible explanation for the difference is that patients knew ionization would be presented with a low-dose control, while light was not. However, the lack of significant association between expectations and treatment response implies that subject bias did not confound assessment of treatment efficacy for the two modalities.

We received no reports of adverse reactions to bright light, although other studies of depression in patients without SAD have reported side-effects including hypomania (Tuunainen *et al.* 2004). Similarly, we found no side-effects for high- or low-density negative ionization, in concurrence with our previous reports for SAD (Terman & Terman, 1995; Terman *et al.* 1998*b*). Such absence of side-effects likely contributed to our near-perfect retention rate across all treatment conditions, rarely seen in drug studies.

Despite the significant group \times time interaction and success rates similar to that seen for SAD, a limitation of the study was its relatively small sample size. Power analysis of the large slope differences found for regression line of SIGH-SAD scores on time indicates a design of twice the size ($n=20$ per group) for power of 0.80 with an α -level of 0.05. The present results, we hope, will motivate patients with chronic depression to participate as research subjects; recruitment for the present study was arduous, reflecting the patients' discouraging earlier treatment experiences.

Light and negative air ion therapies may particularly benefit patients who discontinue, cannot tolerate or show inadequate response to medication. Indeed, we found many cases of remission in patients who had experienced only partial response to drugs, although we could not verify adequacy of the drug trials. With an eye toward enhanced combination treatments, light and ions are candidate adjuncts to drugs and psychotherapy. Recent trials have shown that the combination of light and SSRIs expedites response and increases remission rates relative to drug alone (Benedetti *et al.* 2003; Martiny, 2004; Wirz-Justice *et al.* 2004). Chronic major depression – notoriously difficult to treat with drug monotherapy (Michalak & Lam, 2002) – may likewise be alleviated in combination with bright light, negative air ions or both.

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DECLARATION OF INTEREST

None.

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