ORIGINAL ARTICLE

A Controlled Trial of Timed Bright Light and Negative Air Ionization for Treatment of Winter Depression

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Background: Artificial bright light presents a promising nonpharmacological treatment for seasonal affective disorder. Past studies, however, have lacked adequate placebo controls or sufficient power to detect group differences. The importance of time of day of treatment—specifically, morning light superiority—has remained controversial.

Methods: This study used a morning × evening light crossover design balanced by parallel-group controls, in addition to a nonphotic control, negative air ionization. Subjects with seasonal affective disorder (N = 158) were randomly assigned to 6 groups for 2 consecutive treatment periods, each 10 to 14 days. Light treatment sequences were morning-evening, evening-morning, morning-morning, and evening-evening (10 000 lux, 30 min/d). Ion density was 2.7×10^6 (high) or 1.0×10^4 (low) ions per cubic centimeter (high-high and low-low sequences, 30 min/d in the morning).

Results: Analysis of depression scale percentage change scores showed low-density ion response to be inferior to all other groups, with no other group differences. Response to evening light was reduced when preceded by treatment with morning light, the sole sequence effect. Stringent remission criteria, however, showed significantly higher response to morning than evening light, regardless of treatment sequence.

Conclusions: Bright light and high-density negative air ionization both appear to act as specific antidepressants in patients with seasonal affective disorder. Whether clinical improvement would be further enhanced by their use in combination, or as adjuvants to medication, awaits investigation.

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ARTIFICIAL bright-light therapy for seasonal affective disorder (SAD) alleviates the depressive and reverse neurovegetative symptoms—carbohydrate craving and weight gain, fatigue, and hypersomnolence—that typify patients in winter.[1] Although there have been many demonstrations of clinical improvement,[2,3] 3 major issues remain unresolved: the relative contribution of placebo response, optimum timing of light exposure, and the therapeutic mechanism of action of light.

Despite generally superior response to bright vs dim light and brief-exposure controls,[2,4] using standard light boxes, several recent studies—primarily using head-mounted lighting devices[5-8]—have failed to show bright-light superiority, leaving open a placebo interpretation. Using a novel placebo control for light-box treatment, Eastman and colleagues[9,10] found similar improvement with an inactive negative air ionizer, which further points to the difficulty of establishing treatment specificity.

Chronobiological explanations of pathophysiologic function and treatment, while still not definitive, have provided great impetus to this research. Lewy

See also pages 861, 863, 883, and 890

and colleagues[11] hypothesized a depressogenic effect of wintertime phase delays of the circadian timing system in individuals vulnerable to SAD, which could be counteracted by the antidepressant effect of a phase advance induced by morning light. Although a cross-center analysis suggested that morning light at 2500 lux, 2 h/d, was clinically more effective than evening or midday exposure,[2] individual studies have differed. Studies showing morning superiority used crossover designs,[11-14] while parallel-group studies found no effect of time of day.[10,15-19] In a crossover study using 10 000 lux, 30 min/d, the response to evening light worsened after morning light exposure (but not vice versa).[4] It appeared that the phase advance induced by morning light was coun-

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SUBJECTS AND METHODS

SUBJECTS

Research volunteers (aged 18 to 65 years) were recruited by poster and media announcements and physician referrals, and were screened by a questionnaire that probed for symptoms of winter depression. Candidates received a telephone interview that focused on exclusion criteria (see below). A life history questionnaire followed. Intake evaluations were based on the Structured Clinical Interview for *DSM-III-R*.[24]

Subjects met National Institute of Mental Health criteria for SAD,[1] *DSM-III-R* criteria for mood disorders (itemized below) with seasonal pattern,[25] and criteria for current major depressive episode. They received a physical examination including complete blood cell count with thyroid panel, urinalysis, electrocardiogram, and ocular examination, to verify normal medical status. They were required to abstain from psychotropic medication, alcohol, and recreational drugs. Exclusion criteria included other Axis I disorders, suicide attempt within the past 3 years, and habitual sleep onset later than 1 AM or awakening later than 9 AM.

During 6 years, 158 subjects entered the study and 145 completed it. We present data for 124 subjects who showed relapse (or remained depressed) during a final withdrawal phase. They included 99 women (79.8%) and 25 men (20.2%), aged 18 to 59 years (mean ± SD, 39.4 ± 9.8 years). Diagnoses were major depressive disorder, recurrent, *DSM-III-R* code 296.3, in 71.8% (n = 89); bipolar disorder not otherwise specified, code 296.7, in 23.4% (n = 29); and bipolar disorder, code 296.5, in 4.8% (n = 6).

APPARATUS

The light treatment apparatus (Hughes Lighting Technologies, Lake Hopatcong, NJ; DayLight Technologies Inc, Halifax, Nova Scotia) used SPX-30 triphosphor fluorescent lamps encased in a metal box (27.9 × 58.5 cm) with a translucent plastic diffusing screen. The box was mounted on a height-adjustable stand above the table surface, and tilted downward toward the head at an angle of 30°. The center of the screen was positioned about 32 cm from the eyes, providing light intensity of approximately 10 000 lux. Subjects were instructed to focus on the illuminated area beneath the light source (where they could read), not to look directly at the screen.

The negative air ionizer (16 × 7.5 × 6 cm; JoniCare Model 45; Sea-King AB, Västerås, Sweden) was set on a 100-cm tubular plastic floor stand, approximately 92 cm from the seated subject. It contained 3 wire corona ion emitters with flow rates of 4.5×10^{13} or 1.7×10^{11} ions per second. Resulting air ion densities were approximately 2.7×10^{6} *(high)* or 1.0×10^{4} *(low)* ions per cubic centimeter. The unit was placed 92 cm or more from walls, and away from electrical devices, grounded surfaces, and ventilation ducts. Windows and doors were closed during treatment sessions.

PROCEDURE

The protocol included 6 groups with 2 consecutive treatment periods, each 10 to 14 days long (**Table**). Morning light (M) and evening light (E) were compared in a balanced design with 2 crossover and 2 parallel groups, for detection of potential sequence effects.[20,22] Two parallel groups received morning treatment with high (H)- or low (L)-density negative ions. The habitual sleep pattern, estimated by 1-week averages from daily logs, was the basis for specifying a sleep schedule that accommodated 30-minute treatment sessions in the morning (within 10 minutes of awakening; average, starting about 7 AM) or evening (2 to 3 hours before bedtime; average, starting about 9 PM). Subjects were asked to maintain this schedule throughout the experiment. Napping was discouraged, but permitted if it occurred earlier than 5 ½ hours before bedtime.

teracted by the subsequent phase delay induced by evening light, with consequent blocking of the antidepressant effect.[20,21] Pooled data from 4 centers, using 2500-lux treatment, showed similar results.[20]

The present study compared response to morning and evening light with response to negative air ions. Morning × evening light crossover groups were balanced by parallel groups.[22] The design provided 3 controls for morning light response: a parallel group given evening light, crossovers to and from evening light, and groups given dose-regulated negative air ions (low or high density) in the morning. Previous literature suggests that sustained exposure to negative air ionization might have a mood-elevating effect,[23] but we did not anticipate a clinically significant response given the brief, 30-minute sessions used to match the duration of light exposure.

RESULTS

Figure 1 shows individual rating scale scores across all conditions. The range of baseline scores was 20 to 43; posttreatment scores, 0 to 48. Most data fall below the major diagonal (solid line), indicating general improvement relative to baseline. However, a cluster of data fall on or above the diagonal for crossover subjects who received evening light after morning light (Figure 1, F), indicative of nonresponse or mild worsening. Similarly, there was a preponderance of nonresponders to low-density ions in both treatment periods. At least half of the subjects undergoing light or high-density ion treatment in period 1 improved by 50% or more (points on or below the dashed lines in Figure 1): morning light, 71.7% (33 of 46 subjects); evening light, 66.7% (26 of 39); and high-density ions, 50% (10 of 20). Low-density ions yielded a distinctly lower proportion, 26.3% (5 of 19). Far fewer subjects met the clinical remission criterion of a posttreatment SIGH-SAD score of 8 or less (points below the dotted lines in Figure 1). Within period 1, the remission rate for morning light was 54.3% (25 of 46 subjects); evening light, 33.3% (13 of 39); high-density ions, 20% (4 of 20); and low-density ions, 10.5% (2 of 19).

RATING SCALE MEANS

The Table shows mean depression ratings for all conditions. The SIGH-SAD baseline scores ranged between 27.0 and 29.4 points and were not significantly different across the 6 groups ($F_{5,118} = 0.53$, $P = .80$). While the low-

At the beginning of a 2-week baseline phase, subjects read a description of the rationale for bright-light and negative ion therapies. After both apparatuses were demonstrated, subjects rated expectations for each of 4 potential treatment conditions: morning light, evening light, morning ions, and evening ions (the latter included to balance the questionnaire). Ratings were on a 5-point scale, from no improvement (rating of 1) to full recovery back to normal (rating of 5). Subjects then signed an informed consent, which further described randomization into high- and low-density ion conditions.

At the end of the baseline phase, subjects who met rating scale entry criteria (total score ≥20, Hamilton score ≥10, and atypical symptom score ≥5; see "Depression Ratings," below) were randomly assigned to the treatment groups and were given apparatuses to take home until the end of period 2. They were told that the time of day for treatment might remain the same or change at the start of period 2. Those using ionizers were informed that the density level was not detectable, but a red light signaled when the unit was active. Treatment compliance was monitored by log-in telephone messages.

A 1- to 3-week withdrawal phase followed period 2 treatment to ascertain that clinical improvement was not associated with the expected end-of-season spontaneous remission.[26] Criteria for relapse during withdrawal were the same as for entry at baseline.

The study was conducted between November and March. Within the randomization, there was approximately 1 additional assignment per year to the morning-to-evening light group to increase sample size for a concurrent study with overnight melatonin sampling.

DEPRESSION RATINGS

Symptom severity was assessed by raters blinded to the treatment. We used the Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version (SIGH-SAD),[27] which includes the 21-item Hamilton scale and 8 additional atypical symptoms. Subjects also completed a self-rating version of the SIGH-SAD. If any self-rated item differed from that of the interview by 2 or more points, raters further questioned the subject before determining the final score.

Interrater reliability on the SIGH-SAD was established for 39 patients from previous studies who received 2 independent, same-day, live interviews over the course of 318 consecutive evaluations. Fifteen raters participated. Intraclass correlation coefficients were as follows: SIGH-SAD, $r = 0.95$; Hamilton scale, $r = 0.91$; atypical symptom scale, $r = 0.94$.

STATISTICAL ANALYSIS

Rating scale scores were analyzed in terms of the percentage change from baseline. Analyses of variance (ANOVA) and covariance (ANCOVA) were used to detect group and period effects, group × period interactions, and the influence of baseline regressors.

For categorical response criteria, the difference between proportions in independent groups was evaluated by the Fisher exact probability test and the likelihood ratio χ^2, and for changes within groups by the binomial test. Effect size of proportions was expressed as h; effect size of means, d.[28]

Linear regression, and the correlation coefficient, r, were used to measure the relationship between continuous variables. For all statistical tests, an α level of .05 was set as the criterion for significant differences.

In an exploratory signal detection analysis,[29] a scaled stringency factor was applied to posttreatment and percentage improvement scores to identify ranges with maximal between-group difference. Results were evaluated with the Mann-Whitney U test.[30]

density ion group showed score reductions of about 6 points in both treatment periods, improvement in the other groups ranged between 12.8 points (E2 of M1E2) and 18.1 points (M1 of M1M2). There was a small but significant correlation between baseline and posttreatment scores that accounted for 3.2% of the variance and yielded a difference of 6.4 points (11.9 to 18.3) in expected posttreatment score between the lowest and highest baseline score ($r = 0.18$, $P = .05$, $y = 0.28x + 6.25$).

Group differences were assessed by means of a repeated-measures ANCOVA of SIGH-SAD percentage change scores (Table), including 4 baseline regressors that might influence treatment response: (1) SIGH-SAD score, (2) atypical balance ratio (8-item atypical symptom score divided by total 28-item SIGH-SAD score), (3) time of awakening, and (4) age. Atypical balance has been shown to be a strong predictor of light treatment response in patients with SAD.[31] The main group effect was significant ($F_{5,114} = 7.15$, $P < .001$), with no significant period effect ($F_{1,114} = 0.69$, $P = .41$), but a trend toward a group × period interaction ($F_{5,114} = 2.02$, $P = .08$). Atypical balance was a significant factor ($F_{1,114} = 8.44$, $P = .004$), while the other regressors were not (baseline severity, $P = .11$; time of awakening, $P = .50$; age, $P = .50$). None of the covariates showed a significant interaction with SIGH-SAD percentage change (baseline severity, $P = .82$; atypical balance, $P = .13$; time of awakening, $P = .84$; age, $P = .94$). Although percentage change increased with the atypical balance ratio ($r = 0.28$, $P < .001$), accounting for 7.8% of the variance, there were no significant between-group differences in the ratio (range, 0.42 ± 0.10 to 0.47 ± 0.10; $F_{5,118} = 0.59$, $P = .70$).

A Dunnett post hoc comparison[32] showed that the putative placebo control group (L1L2) improved significantly less than all 5 active treatment groups ($P < .03$). Furthermore, the 5 groups did not differ between each other ($F_{4,96} = 0.90$, $P = .47$). When compared with placebo in period 1, morning light (pool of M1 from M1M2 and M1E2) showed an advantage (by subtraction) of 39.7%, with a large effect size ($d = 1.35$); evening light (pool of E1 from E1E2 and E1M2) showed an advantage of 35.0% ($d = 1.26$); and high-density ions showed an advantage of 22.0%, with a medium effect size ($d = 0.67$). By the end of period 2, the advantage of high-density ions approximately matched that of light (34.6%, $d = 0.95$).

Our a priori hypothesis, based on earlier research,[4,20] was of a selective decrease in response to evening light

Depression Ratings and Posttreatment Change

	Time of Light Treatment				Negative Ion Dose*	
Period 1 Period 2	Morning (M1) Morning (M2)	Evening (E1) Evening (E2)	Morning (M1) Evening (E2)	Evening (E1) Morning (M2)	High Density (H1) High Density (H2)	Low Density (L1) Low Density (L2)
Sample size	19	19	27	20	20	19
Raw score†						
Baseline	28.6 ± 4.3	29.4 ± 6.4	29.2 ± 5.4	27.0 ± 4.2	29.3 ± 6.6	28.3 ± 6.2
Period 1	10.5 ± 7.6	14.1 ± 7.8	12.0 ± 9.1	10.7 ± 6.4	15.8 ± 8.8	22.3 ± 9.2
Period 2	12.6 ± 6.4	12.0 ± 9.1	16.4 ± 11.5	8.9 ± 9.0	13.7 ± 9.6	22.7 ± 9.1
Change, %						
Period 1	63.4 ± 26.1	50.9 ± 28.8	57.8 ± 30.5	59.8 ± 23.0	42.4 ± 34.6	20.4 ± 31.0
Period 2	55.8 ± 32.4	58.9 ± 29.5	44.0 ± 37.6	68.1 ± 26.0	50.3 ± 37.3	15.7 ± 35.5
Remission rate‡						
Period 1	52.6 ± 19.2	31.6 ± 17.4	55.6 ± 15.9	35.0 ± 17.9	20.0 ± 15.0	10.5 ± 11.9
Period 2	47.4 ± 19.2	36.8 ± 18.1	25.9 ± 14.1	65.0 ± 17.9	40.0 ± 18.4	5.3 ± 8.8

**Morning treatment.*

†On the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version (mean ± SD), which includes the 21-item Hamilton Depression Rating Scale plus 8-item atypical symptom scale.

‡Percentage of cases (±95% confidence interval) with posttreatment score ≤8. Subjects who met this response criterion showed 83.0% ± 9.7% improvement (range, 66.7%-100.0%).

after morning light treatment. Indeed, ANCOVA for the 4 light treatment groups showed a significant group × period interaction ($F_{3,77} = 2.79$, $P = .05$) located to the M1E2 sequence in the balanced comparison (M1E2 vs E1E2; $F_{1,40} = 6.01$, $P = .02$). By contrast, the opposite sequence showed no such interaction (E1M2 vs M1M2; $F_{1,33} = 1.26$, $P = .27$), and the direct crossover showed only a trend (M1E2 vs E1M2; $F_{1,41} = 3.50$, $P = .07$).

CATEGORICAL REMISSION RATE

Examination of the morning × evening crossover by means of a strict, discrete remission criterion—posttreatment SIGH-SAD score of 8 or less—leads to a contrasting conclusion. In **Figure 2**, a scatterplot of posttreatment scores for the crossover groups indicates that 68.1% (32/47) of subjects responded to light at one or both times of day. Only 31.3% (10 of 32 subjects) responded nondifferentially. Among differential responders, there was a ratio of 4.5:1 in favor of morning light (81.8% [18 of 22]; evening light, 18.2% [4 of 22]; $P = .002$, binomial test).

The 4-group summary in **Figure 3** shows that morning light maintained a consistently superior effect (47.4% to 65.0% remissions) to evening light (25.9% to 36.8% remissions) regardless of sequence within parallel and crossover groups. When groups that received the same treatment in period 1 were pooled, the remission rate for morning light was 54.3% (25 of 46 subjects), while the rate for evening light was 33.3% (13 of 39; $P = .04$, Fisher exact test), which yields a morning light advantage of 21.0% ($h = 0.43$, medium effect). Furthermore, in both crossover sequences, morning light was superior to evening light (M1E2, 29.7% advantage; E1M2, 30.0% advantage; likelihood ratio $\chi^2_1 = 9.49$, $P = .002$).

The groups showed greater differentiation by categorical criteria than they did by percentage change. In period 1, the advantage of morning light over placebo was 43.8% (n = 46, $h = 1.0$, large effect); evening light, 22.8% (n = 39, $h = 0.57$, medium effect); and high-density ions, 9.5% (n = 20, $h = 0.27$, small effect). By the end of period 2, the remission rate for high-density ions increased from 20.0% to 40.0% (Fisher exact test, $P = .01$), yielding a relative advantage of 34.7% relative to placebo ($h = 0.91$, large effect).

CLINICAL RESPONSE CRITERIA AND DETECTABILITY OF THE MORNING-EVENING DIFFERENCE

In this section, we introduce a signal detection analysis that reconciles the discrepancy between the ANCOVA of change scores and categorical identification of remissions. Estimation of remission rate varies with stringency of the criterion, eg, posttreatment SIGH-SAD score of 8 or less *(stringent)*[33] or 14 or less *(lax)*.[20] The signal detection method consecutively scales the range of posttreatment scores and percentage change to specify relative response rates across all possible criteria.

Figure 4 compares the results for morning and evening light groups (period 1, n = 85). The major diagonal, with slope = 1.0, describes the line for nondifferential response ("chance"). When a series of points systematically deviates from the diagonal—rising gradually from it, reaching a maximum, then converging back on it—the curve as a whole may differ from chance. The area under the curve is compared with the area under the diagonal by a Mann-Whitney *U* test of scores falling within the curve's range.

Using the dependent measures of posttreatment SIGH-SAD score and percentage change adjusted for the baseline regressor, the signal detection plots closely superimpose such that we can map one variable onto the other (eg, posttreatment scores ≤14 coincided with change ≥50%). Over the entire data set, there was no significant morning-evening difference, in agreement with the ANCOVA for change scores. However, there are distinct ranges (posttreatment score, 4-17 [54 of 85 cases]; change, 40%-85% [52 of 85 cases]) in which the curves systematically deviate above the major diagonal, indicating morning light

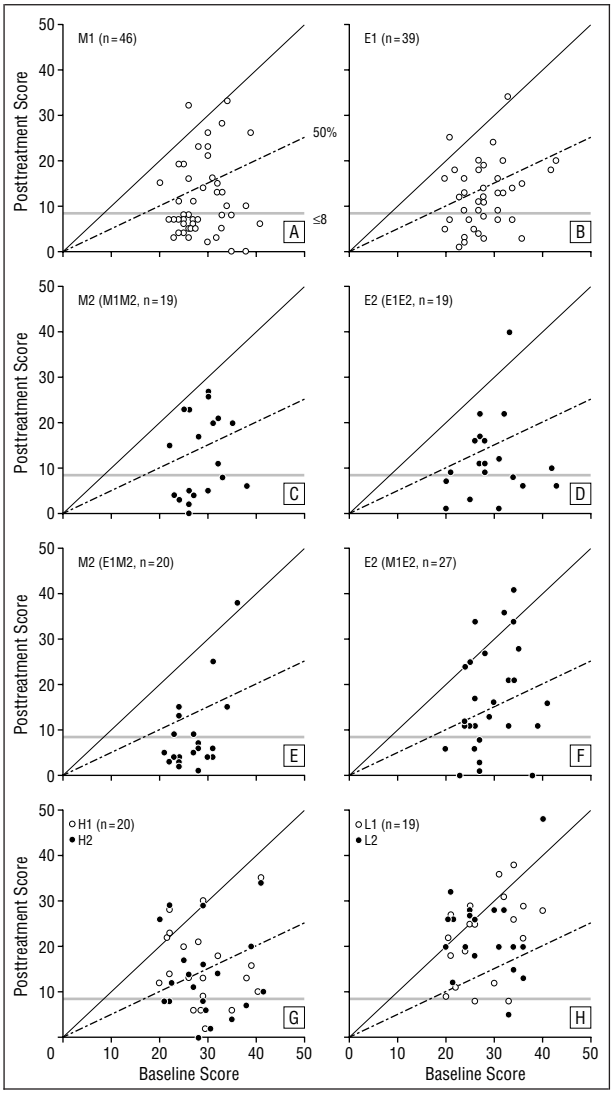

Figure 1. *Scatterplots of individual subjects' depression scale (Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version) scores at baseline and after 2 consecutive treatment periods (open circles, period 1; closed circles, period 2). Overlapping data are displaced by 0.5 point (baseline score). Solid line (major diagonal) indicates absence of pretreatment to posttreatment change; dashed line, 50% improvement relative to baseline; area below dotted line, posttreatment score of 8 or less (a criterion for clinical remission). Light treatment groups are pooled in period 1 (M1 [morning] or E1 [evening], A and B). For period 2, the groups are separated according to parallel (C and D) or crossover (E and F) sequences. High (H)- and low (L)-density ion data are superimposed across parallel-group sequences (H1H2 and L1L2, G and H).*

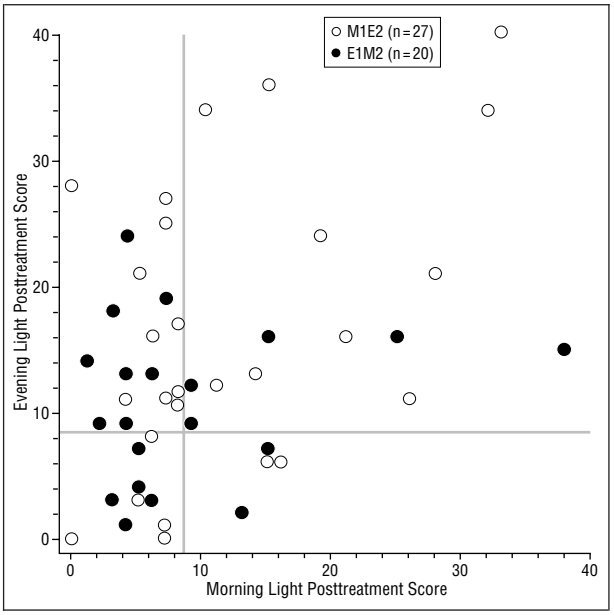

Figure 2. *Scatterplot of posttreatment depression scale scores for subjects who received morning light (M) and evening light (E) treatment in crossover groups (M1E2, E1M2). Overlapping data are displaced by 0.5 point. Dashed lines divide the Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version score ranges of 8 or less (responders) and greater than 8 (nonresponders). Data points falling into the lower left quadrant are from subjects who responded to both morning and evening light; upper right quadrant, nonresponders to both. Upper left quadrant includes exclusive responders to morning light; lower right quandrant, evening light.*

superiority (posttreatment score, $P = .02$; change, $P = .03$; Mann-Whitney U tests). The groups were maximally differentiated for posttreatment scores in the range of 7 to 12, or 60% to 75% change. Given extremely stringent response criteria (≤4 points, ≥85%; n≤14), the groups did not differ. Given extremely lenient criteria (≥17 points, ≤40%; n≤20), the negative deviation from the diagonal indicates that evening-light subjects predominated among nonresponders.

EXPECTATIONS AND BIAS

An ANOVA was performed to determine whether expectations for period 1 treatment success differed between those who received morning or evening light, or low- or high-density ions. Although ratings were higher for light than for ions (M1, 3.85 ± 0.90; E1, 3.75 ± 0.85; H1, 2.90 ± 0.97; L1, 2.84 ± 1.17; $F_{3,120} = 8.88$, $P < .001$), the difference was only about 1 point on the 5-point scale, in the range of moderate (3) to major (4) improvement.

Expectation ratings within groups were not significantly correlated with treatment response. There was, however, a positive trend when results were pooled across all treatment conditions ($r = 0.15$, n = 124, $P = .09$), which can be attributed to lack of response in subjects given low-density ions. Interestingly, the correlation within the low-density ion group was nearly zero ($r = 0.01$, n = 19, $P = .97$), which indicates that variation in response to placebo was not influenced by expectations.

Although mean expectations for morning and evening light did not differ, individual subjects might show a bias toward either time of day, which could influence their response. We calculated within-subject bias scores by subtracting the expectation rating for evening light from that for morning light. An ANCOVA on posttreatment percentage change scores, with bias score as the regressor, showed no significant morning-evening group ($F_{1,70} = 0.79$, $P = .38$) or bias ($F_{1,70} = 2.14$, $P = .15$) effect.

Such within-subject bias might have greater influence on the response to high-density ions, since, on average, expectations were higher for light. Indeed, 65% (13) of 20 subjects who received high-density ions showed a bias toward morning light, while only 5% (1 of 20) showed a bias toward ions. Nevertheless, there was no significant correlation between bias score and high-

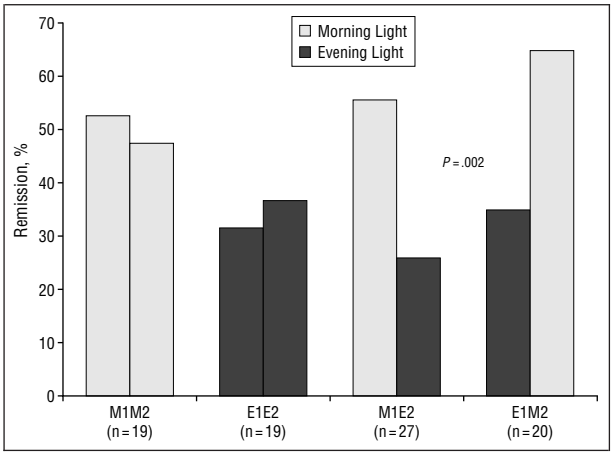

Figure 3. *Remission rates (posttreatment Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version score ≤8) for the 4 light treatment groups (morning [M] or evening [E]) across periods 1 and 2. The symmetrical crossover interaction was confirmed by a likelihood ratio χ^2 test.*

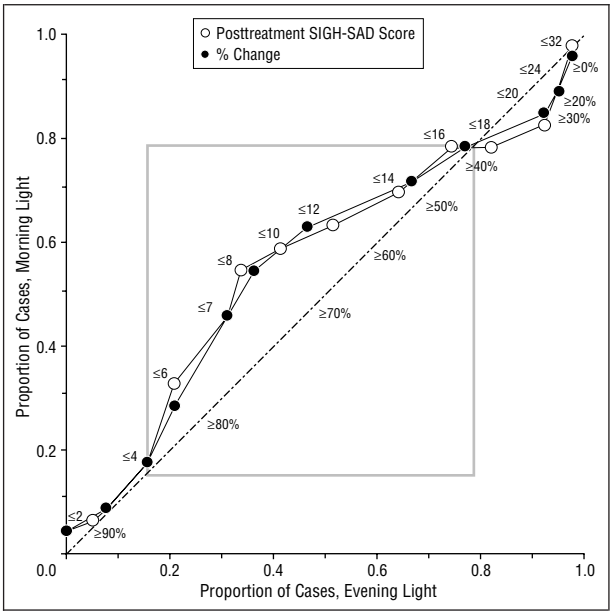

Figure 4. *Signal detection plot of proportion of subjects reaching successively stringent response criteria under morning (M) or evening (E) light in period 1 (M1, n = 46; E1, n = 39). The major diagonal defines a "chance line" along which response proportions are equal. Dotted lines enclose a region of positive deviation from the diagonal, indicating morning light superiority. SIGH-SAD indicates Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version.*

density ion response in either treatment period (both $r = 0.09$, n = 20, $P = .70$).

TIMING OF SLEEP

At baseline, there were no significant differences among the 6 groups in the times of sleep onset (mean ± SD, 23.66 ± 0.90 hours), awakening (7.32 ± 0.97 hours), nocturnal sleep duration (7.52 ± 0.78 hours), or total duration, including naps (7.70 ± 0.78 hours). We compared sleep patterns in period 1 by pooling data for morning light (n = 39), evening light (n = 37), and negative ions (n = 36; high- and low-density results did not differ). An ANOVA of sleep measures showed that the only effect of treatment was on wake-up time. Subjects given morning light awakened 0.62 ± 0.62 hours earlier than at baseline; negative ions, 0.41 ± 0.37 hours earlier; and evening light, 0.09 ± 0.58 hours earlier ($F_{2,109} = 9.09$, $P < .001$). Post hoc tests showed no significant difference between morning light and ion groups, but both awakened significantly earlier than under evening light (morning light, $F_{1,74} = 14.39$, $P = .003$; ions, $F_{1,71} = 7.61$, $P = .007$). The mean advance in wake-up time closely matched the 0.5-hour session duration.

COMMENT

This study provides evidence of the specific efficacy of bright light and high-density negative air ionization. Although we did not use an inert placebo, low-density ions were ineffective in comparison with 3 putative active conditions, bright light in the morning or evening and high-density negative ions. Each of these treatments attained approximately a 30% advantage over low-density ions—as gauged by the difference in percentage improvement—and provided clinically significant relief, with greater than a 50% reduction in depressive symptoms. Remission rate for high-density ions increased with an additional 10 to 14 days of treatment after period 1; no corresponding changes were found for the parallel light groups, which contrasts with studies showing improvement over 3 to 4 weeks.[33,34] The superiority of morning over evening light was most evident, according to signal detection analysis, given remission criteria in the range of 60% to 75% improvement, or posttreatment SIGH-SAD score of 7 to 12. Nonetheless, some subjects responded preferentially to evening light, and the group average result should not disguise a need to determine optimum timing for individual patients.

Our study expands on previous morning × evening crossover comparisons by the addition of balanced parallel groups, thus enabling interpretation of sequence effects with controls for previous treatment. The SIGH-SAD scores decreased when evening light followed morning light, while the opposite sequence showed no significant change, confirming our earlier studies[4,20] and our analysis[21] of early data of Lewy and Sack. When we applied a stringent categorical remission criterion, however, morning light produced higher response rates in both crossovers, a result that supports recent data of Lewy and colleagues.[35] Nonetheless, since evening light produced a response superior to the low-density ion placebo, we cannot conclude that evening light is inactive.

The superiority of morning light is plausibly explained by chronobiological effects that vary with time of day.[11,14,35] In the present study, remission rate was highest after the evening-to-morning transition (65.0%; Table) and lowest after the morning-to-evening transition (25.9%). Indeed, in a subset of the subjects whose melatonin was sampled, we found that the largest phase advances also occurred after the evening-to-morning transition, and the largest delays after the morning-to-evening transition.[36,37] Circadian phase (melatonin onset), wake-up time, and depression rating scale measures appear to be interrelated. Multivariate ANOVA of morn-

ing × evening light crossover groups showed a significant group × period interaction ($F_{1,28} = 16.09$, Wilks $\lambda = 0.64$, $P = .004$), which implies that the 3 variables respond in concert.

Expectations within the light groups were similar, which strengthens the conclusion that morning light was differentially active. Likewise, expectations within the ion groups were similar, which strengthens the conclusion that the higher dose was differentially active. Although expectation ratings were not significantly correlated with clinical response, ratings for ions were generally lower than for light. Most likely, this reflects subjects' greater familiarity with claims about light therapy. Cross-modality contrasts of efficacy (light vs ions), and sufficiency of low-density ions as a placebo control for light, are thus complicated by unequal expectation ratings.

One recent study that matched pretreatment expectations in groups receiving bright light and an inert placebo (inactive negative ion generator) found morning light superior to placebo, but only when a strict remission criterion was used.[33] However, no morning-evening or evening-placebo differences were detected. Another recent trial of morning and evening light, without a placebo, showed better response to morning light, but the remission rate was low.[35] Although expectation ratings were not significantly correlated with clinical response, they were significantly higher for morning light. A parallel group study, with matched expectation ratings but without a placebo, found no significant morning-evening difference.[17] The authors attributed the lack of effect to high severity of depression, based on a cross-center analysis that found morning light superiority only in milder cases.[2] However, severity in that study and in ours was similar; the main distinction was in the atypical balance ratio (theirs, 0.29 ± 0.10; ours, 0.44 ± 0.10; $P<.001$, 2-tailed t test). We have suggested that the specific efficacy of light is more likely to be detectable in patients with high atypical balance.[31]

A potential confound in our study was the minor advance in wake-up time—approximately equal to the 30-minute session duration—when subjects received morning treatments. It appears that most subjects adjusted their wake-up time to accommodate the morning treatment session. The advance in wake-up time was observed in morning light and ion groups alike, including the low-density ion placebo group, which showed minimal improvement. Thus, it is unlikely that wake-up time per se was responsible for group differences in clinical response. Furthermore, since sleep duration did not change significantly, we cannot attribute improvement to sleep deprivation.[38,39]

Our finding of clinical improvement under high-density negative ion treatment was unexpected, although there have been numerous anecdotal reports of mood enhancement with increased negative ion concentration.[40] We have monitored potential side effects of negative air ionization, using a comprehensive checklist,[41] and found no emergent symptoms or differences between low- and high-density groups. The effective range and optimum dose remain uncertain. High ion flow rate may be needed to override uncontrolled modulating environmental factors, such as relative humidity, room size, and the proximity of grounded objects. The mechanism of action of negative air ionization is unknown. It is even unclear how the charge could be biologically transduced. The active agent may be a by-product such as the direct-current electrical field or oxidative gases (eg, nitric oxide). Early animal and human studies implicated serotonergic mechanisms—as reflected, for example, by changes in 5-hydroxyindoleacetic acid excretion—but results were inconclusive and faulted for lack of controls.[23]

We conclude that light therapy acts as a specific antidepressant in SAD, and morning treatment is most effective. High-density negative air ionization also appears to have a specific antidepressant effect. If the latter result is sustained in replications, the method may serve as an alternative or adjunct to light therapy and medications.

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