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Controlled trial evaluation of exposure duration to negative air ions for the treatment of seasonal affective disorder

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ABSTRACT

This study evaluated the effectiveness of 30 or 60 min of daily exposure to high-density or to zero-density (placebo condition) negative air ions over 18 days on the symptoms of seasonal affective disorder (SAD) in 40 participants under controlled laboratory conditions. Exposure to high-density negative air ions was superior to zero-density negative air ions in alleviating depression and the atypical symptoms of SAD. Also, more subjects in the high-density negative air ions groups met two different clinical response criteria than did those in the zero-density groups. Within the high density treatment group, both the short and long daily exposure reduced SAD symptoms. Exposure to negative air ions produced no negative side effects, and no ozone was produced by the ion generators. In both the high-density negative air ions and zero-density negative air ions groups, a significant placebo effect was found for most clinical measures. Finally, for the high-density negative air ion groups, subjects with a morningness chronotype responded better to treatment with high-density negative air ions than did those with an eveningness chronotype.

1. Introduction

Seasonal affective disorder (SAD) is a recurrent mood disorder with a characteristic pattern of onset and remission that has been classified as a variant of major depressive disorder (American Psychiatric Association, 1994). Episodes of SAD occur predominantly in fall and winter and are characterized by symptoms of depression as well as atypical symptoms including excessive sleep, craving for carbohydrates, irritability, social withdrawal, daytime fatigue, and loss of concentration (Rosenthal et al., 1984). In addition to antidepressant medications (Lam et al., 2006) and exposure to bright light SAD (Terman and Terman, 2005), exposure to high-density negative air ions has been found effective for treating SAD (Flory et al., 2010; Perez et al., 2013; Terman and Terman, 1995, 2006; Terman et al., 1998).

Although high levels of negative ionization are superior to low levels for treating seasonal or chronic depression (Perez et al., 2013), no studies have systematically compared the antidepressant effects of long versus short daily exposures to negative air ions on the symptoms of SAD. For the major non-pharmacological treatment for SAD, morning bright light exposure, longer treatment duration has been associated with greater improvement in symptoms (Checkley et al., 1986; Terman et al., 1989a, 1989b; but see Wehr et al., 1986). Light therapy both improves the depressive and atypical symptoms of SAD and acts to phase advance circadian rhythms (Wirz-Justice, 2009). The physiological mechanism of action of negative ions is unknown (Kinne, 1997; Terman et al., 1998), and it is unclear if longer daily exposure would influence treatment response. In a meta-analysis of several experiments, Perez et al. (2013) reported no dose-response effect between total exposure time to negative air ions over entire treatment time (in hours) and posttreatment depression severity in subjects with SAD.

The present study utilized a parallel-group design to evaluate the efficacy of two daily exposure durations (30 min and 60 min) of high-density negative air ions (HDNI) compared to the same two daily durations of zero-density negative ions (PLCB, the placebo) for treating SAD. As in the investigation of the effects of light, negative air ions, and auditory stimuli on mood changes (Goel and Etwaroo, 2006), all participants in this study received daily treatments in a controlled laboratory setting; unlike previous studies, we were able to directly measure both air ionization and ozone levels in treatment rooms during and after daily exposure sessions.

Based on previous research (Flory et al., 2010; Perez et al., 2013; Terman and Terman, 1995, 2006; Terman et al., 1998), we predicted that both the 30-min and the 60-min active treatment with HDNI would result in greater alleviation of SAD symptoms than would either PLCB

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group. We predicted that the 60-min HDNI treatment would have greater efficacy in alleviating SAD symptoms than would the 30-min HDNI treatment. Finally, we assessed the relationship between chronotype, e.g., morningness and eveningness, and levels of depression and SAD symptoms, because an eveningness chronotype has been associated with various mental disorders (Fares et al., 2015).

2. Methods

2.1. Subjects

A total of 41 female students and staff at Hollins University in Roanoke, an all-women's university in Virginia (latitude 37° 16′, North; average sunrise time approximately 0732 during January) and one male staff relative participated in this study that was conducted during the months of January 2009 and 2010. Of these original 42 participants, two voluntarily withdrew from the January 2010 study. The final group, none of whom had prior experience with negative air ion therapy, included 37 white and 3 black subjects ranging in age from 18 to 55 years (M = 24.8 years; $S.D.$ = 10.5 years). A request for subjects was communicated in a campus-wide media announcement prior to each study. Respondents to this announcement completed the Seasonal Pattern Assessment Questionnaire (SPAQ: Rosenthal et al., 1987), a retrospective self-report rating of pattern and degree of seasonal variation in sleep, social activity, mood, body weight, appetite, and energy level. The global seasonality score (GSS), derived from categorical scales of mood and behavior, ranges from 0 to 24. To meet the initial screening criteria for inclusion in this study, a respondent was required to score the following on the SPAQ: a GSS of at least 12, a winter pattern (feels worse, eats more, socializes less, and sleeps more in winter months than in summer months), and a rating of at least "moderate" personal discomfort [a score of 2 on a scale that ranges from 1 (*mild*) to 5 (*debilitating*)] as a result of these seasonal changes.

Subjects were instructed to maintain pre-established prescription medication regimens, if any, throughout the 18 consecutive treatment sessions and during the week prior to the study and to also document that these regimens were unchanged in a posttreatment questionnaire. None of the subjects changed medications or dosages during the study. Of the 40 subjects, 12 remained on prescribed medications other than psychotropic drugs, and 11 remained on a psychotropic medication regimen of one or more of the following: a selective serotonin reuptake inhibitor, a norepinephrine/dopamine reuptake inhibitor, a serotonin modulator, an anxiolytic, or a combination of two or more of these psychotropic medications. During both January studies, each participant received a monetary incentive stipend of $150 for remaining in the 18-consecutive day study, and one of these subjects received an additional $100 in a random lottery drawing. The two participants who withdrew from the study were each provided a pro-rated stipend. Subjects read and signed a written informed consent form after the document was fully discussed with them. The study received institutional approval from the Hollins University Human Research Review Committee.

2.2. Apparatus

2.2.1. Negative air ion generators and treatment rooms

Six negative ion generators (Model VI-2500, SphereOne, Inc., Silver Plume, CO, USA), each measuring 19.7 cm by 7.6 cm, were located in six similar treatment rooms with dimensions of approximately 2.0 m by 3.0 m by 2.5 m. Each generator was placed on a 76.0-cm high table and was positioned ~ 46.0 cm to one side of a portable DVD player screen in front of the participant. The ion output of each of the six generators was measured using AlphaLab Air Ion Counters (AlphaLab, Inc., Salt Lake City, UT, USA) by a physicist (JA). Three generators that emitted ~ 2.0×10^6 ions/cm^3 at the subject's sitting distance of ~ 60 cm from the generator served as the high-density negative air ion (HDNI) treatment devices. The remaining three generators, modified to emit a zero level of negative air ions, served as the placebo (PLCB) treatment devices. A grounded wrist strap on each generator maximized ion flow toward the subject's body, and doors to the treatment rooms were closed during daily sessions. The ambient level of negative air ions in each of the six treatment rooms was ~ 2.0×10^3 ions/cm^3. A warning sign was placed on each generator to decrease the possibility that participants would touch the generator's corona emitter wand and, thereby, receive feedback as to their treatment condition. During periodic observation of subjects during treatment sessions, there was no indication that any of them touched the emitter wand.

2.2.2. Ozone measuring device

Prompted by recent safety concerns associated with the use of high-density negative ion generators (Waring and Siegel, 2011), ozone levels were measured with an ECO ozone meter (Model EZ-1X, Eco Sensors, Inc., Santa Fe, NM, USA) at various locations within each treatment room during negative air ion generator operation. Measurements of different areas within the treatment rooms were necessary because ozone levels can vary greatly within a closed space.

2.3. Treatment assessment inventories

2.3.1. Systematic Assessment for Treatment Emergent Effects (SAFTEE)-self-rating version

The self-rating version of the SAFTEE, an adaptation of the original comprehensive interview (National Institute of Mental Health, 1986), incorporates a 5-point checklist format for each of 132 questions to detect and assess the strength of adverse physical and psychological side-effects of clinical treatments.

2.3.2. Treatment Expectation Questionnaire (TEQ)

This self-report scale, modeled on the concepts of Borkovec and Nau (1972), provides a rating, ranging from 0 to 4, of the subject's belief of benefit from completing the assigned treatment, the expectation that the treatment would make symptoms worse (reverse scored), the belief that the treatment was logical, and the degree of comfort in recommending the treatment to a friend with SAD. Data from all four questions on the TEQ were used for analysis, with total scores ranging from 0 to 16 and higher scores corresponding to greater expectation of treatment benefits.

2.3.3. Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version–Self Rating (SIGH-SAD-SR)

The SIGH-SAD-SR consists of two scales: a structured interview for the 21-item Hamilton Depression Rating Scale (HAM-D) and an 8-item scale that assesses the atypical characteristics of SAD (ATYP8) (Williams et al., 1998) including hypersomnia, hyperphagia with associated weight gain, and daytime fatigue. Previous studies (Terman and Terman, 1995; Terman et al., 1998) reported that both scales of the SIGH-SAD-SR were of value in determining treatment response to bright light as well as to negative air ions. The self-rating version of the SIGH-SAD (SIGH-SAD-SR) has been shown to produce results consistent with the interview-administered version (Terman and Williams, 1994; Terman et al., 2001) and has been used as a primary measure of seasonal depression (Partonen et al., 1993, 1998; Wileman et al., 2001) and nonseasonal depression (Ando et al., 1999; Loving et al., 2002; Leppämäki et al., 2004).

2.3.4. Beck Depression Inventory (BDI)

The BDI (Beck et al., 1961) is designed to assess the severity of depression in adolescents and adults and has been validated in college populations (Bumberry et al., 1978: Goel and Grasso, 2004). Each of the 21 multiple-choice questions on the BDI consists of a 4-point scale ranging in symptom severity from 0 to 3. Total scores of 0–9 are within the minimal range, scores of 10–16 indicate mild depression, scores of

17–29 indicate moderate depression, and scores of 30–63 indicate severe depression.

2.3.5. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for seasonal affective disorder

As specified by the DSM-IV (American Psychiatric Association, 1994), the criteria for Major Depressive Episodes in Bipolar I Disorder, Bipolar II Disorder, or Major Depressive Disorder, Recurrent, With Seasonal Pattern include (1) a history of either bipolar disorder (manic depressive disorder) or major depressive disorder (unipolar depression with episodes of mania), (2) depression, over the past 2 years during particular, predictable seasons of the year, (3) no other depressive episodes outside of recurrent seasonal episodes of depression over the past 2 years, and (4) more episodes of seasonal than nonseasonal depression throughout the individual's lifetime.

2.3.6. Morningness-Eveningness Questionnaire (MEQ)-revised

The revised MEQ, a partially rephrased version of the original instrument (Horne and Östberg, 1976), incorporates discrete-item choices for each of 19 questions to assess an individual's preference for either morning or evening patterns of activity. Scores range from 16 to 86, with lower scores indicating eveningness chronotype and higher scores indicating morningness chronotype.

2.4. Inclusion criteria

Each respondent having met the initial SPAQ screening criteria 6 weeks prior to the beginning of the study was required to complete the SIGH-SAD-SR, BDI, MEQ, SAFTEE, and a DSM-IV criteria checklist within 24 h prior to the first treatment session. To qualify for inclusion in the study, a respondent was required to score at least 20 points on the overall SIGH-SAD-SR in the pretreatment assessment, including a score of at least 10 on the Hamilton Depression Rating Scale and a score of at least 5 on the Atypical Symptom Scale (Terman et al., 1990). Respondents were also required to meet each of the four DSM-IV criteria for SAD by answering “yes” to the four questions provided in a symptom checklist derived from the Criteria for Seasonal Pattern Specifier (DSM-IV, p. 291). No pretreatment criterion score was required on the BDI, MEQ, or SAFTEE, although the pretreatment BDI indicated that 37 of the 40 subjects (93%) showed at least moderate depression.

2.5. Procedure

During January 2009 and 2010, data were collected when the daily photoperiod was relatively short. A four-group, pretreatment/midtreatment/posttreatment design was used. Subjects were randomly assigned to one of four treatment conditions: 30-min high-density air ions (HDNI 30′: $n = 10$), 60-min high-density air ions (HDNI 60′: $n = 10$), 30-min placebo (PLCB 30′: $n = 11$), or 60-min placebo (PLCB 60′: $n = 9$). Participants were informed that they had a 1 in 2 (50%) chance of being assigned to either a bona fide treatment condition or to a placebo treatment condition. The four treatment descriptions were worded as similarly as possible. On the first treatment day, prior to the initial treatment session, each subject was seated in front of an ion generator and was asked, after discussion of the study, to read and sign a written informed consent form that included a description of the treatment. This description indicated that published research studies of negative ionization as a treatment for SAD have found no emergent risks or side effects associated with this treatment for SAD. Subjects were then asked to complete the TEQ.

Each subject was provided either a 30-min or a 60-min treatment session between 0745 and 1345 in one of six nearly identical treatment rooms. Subject treatment schedules remained constant across the 18 consecutive days of the study. During sessions, subjects could watch movies on DVD players, listen to music, read, use a cell phone or personal computer, or rest quietly.

Within 24 h of completion of the 9th treatment session (midtreatment assessment), subjects completed the SIGH-SAD-SR, BDI, MEQ, and SAFTEE. Within 24 h of completion of the 18th treatment (posttreatment assessment), subjects once more completed each of these four inventories and also completed a questionnaire to affirm they had maintained their medication regimens. Finally, subjects were told the nature of the study, including the group they were in, and were given the opportunity to ask questions about the study.

3. Results

3.1. Ion and ozone measurements

The three active high-density negative air generators emitted $\geq 2.0 \times 10^6$ ions/cm^3 at the subject's sitting distance of $\sim$ 60 cm from the generators. The other three modified generators emitted a zero level of negative air ions against an ambient negative air ions level of $\sim 2.0 \times 10^3$ ions/cm^3. In the treatment rooms, there was no measurable change in ion dose received by the subjects in the presence of electronic devices such as DVD players, cellphones, or laptops. Furthermore, no measurable ozone was detected from any of the negative ion generators at any location within treatment rooms.

3.2. SAFTEE measures

To make analyses more manageable, the 132 items included within the SAFTEE inventory were organized into 17 categories and analyzed using a series of 3 (Treatment phase: pretreatment, midtreatment, posttreatment) × 4 (Treatment group: PLCB 30′, PLCB 60′, HDNI 30′, HDNI 60′) mixed model ANOVAs. The side-effect categories included (1) head; (2) eyes; (3) ears; (4) mouth and teeth; (5) nose and throat; (6) chest; (7) heart; (8) stomach and abdomen; (9) bowel; (10) appetite; (11) urination; (12) menstrual period; (13) sexual function; (14) muscles, bones and joints; (15) walking and movement; (16) scalp and skin; and (17) thinking, mood, and energy. Two major patterns were found from these analyses. First, for no category were significantly more side effects reported for the active treatments (HDNI 30′ and HDNI 60′) than for the placebo treatments (PLCB 30′ and PLCB 60′). This finding indicates that treatment with high-density negative air ions had no appreciable negative side effects. Second, a significant main effect of treatment phase in 16 of the 17 categories was found. Specifically, participants in all four groups showed a decrease in the number of reported negative side effects from pretreatment to posttreatment assessment. This finding indicates a strong placebo effect for both active and placebo conditions. No significant treatment group by treatment phase interactions were found.

3.3. Pretreatment expectations

No significant group differences were found in pretreatment expectation scores on the TEQ (Kruskal-Wallis Test; H [3, $N = 40$] = 5.70, $P = 0.13$). The median treatment expectation scores, with higher scores representing a greater expectation of benefit, were 11 in the PLCB 30′ group ($IQR = 2$), 10 in the PLCB 60′ group ($IQR = 3$), 8 in the HDNI 30′ group ($IQR = 4$), and 9 in the HDNI 60′ group ($IQR = 3$). In addition, there were no significant Spearman rho correlations between TEQ scores and percent improvement from pretreatment to posttreatment in total SIGH-SAD-SR scores (HDNI 30′: $r_s(8) = -0.32$, $P = 0.37$; HDNI 60′: $r_s(8) = 0.41$, $P = 0.24$; PLCB 30′: $r_s(9) = 0.009$, $P = 0.98$; PLCB 60′: $r_s(7) = -0.25$, $P = 0.52$; total sample: $r_s(38) = 0.02$, $P = 0.89$), showing that pretreatment expectations were not significantly related to actual improvement.

3.4. Effects of psychotropic medication regimens

Because of possible interactions between medication regimens and

negative air ion treatment for SAD (Thorell et al., 1999), we assessed how treatment affected participants who were (n = 11; 27.5%) or were not (n = 29; 72.5%) taking psychotropic medications. All participants maintained their medication regimes throughout treatment. The percentage of participants taking a psychotropic medication for each group was as follows: 20% in the HDNI 30′ group, 20% in the HDNI 60′ group, 45% in the PLCB 30′ group, and 22% in the PLCB 60′ group. A 2 (Taking or not taking medication) × 4 (Treatment group) factorial ANOVA was used to assess potential differences in percent improvement on the total SIGH-SAD-SR score. No significant main effects were found for medication regimen, F (1, 32) = 0.03, P = 0.86 or for group, F (3, 32) = 1.29, P = 0.30, and there was no medication regimen by group interaction, F (3, 32) = 0.38, P = 0.77.

3.5. Scheduled treatment time and percent improvement in SIGH-SAD-SR total score

Pearson correlations between treatment session onset time and percent improvement in the SIGH-SAD-SR total score were not significant for any treatment group (HDNI 30′: r(8) = 0.60, P = 0.06, r^2 = 0.36; HDNI 60′: r(8) = − 0.10, P = 0.77, r^2 = 0.01; PLCB 30′: r(9) = 0.08, P = 0.80, r^2 = 0.006; PLCB 60′: r(7) = − 0.49, P = 0.18, r^2 = 0.24). Similarly, the correlation for all 40 subjects was also not significant, r(38) = − 0.07, P = 0.68, r^2 = 0.005. Daily timing of treatment session was not strongly associated with overall improvement of SAD symptoms, but there was a small to moderate effect size found for the HDNI 30′ group.

3.6. Length of exposure to ions

Initial 3 (Treatment phase: pretreatment, midtreatment, posttreatment) × 2 (Treatment group: HDNI, PLCB) × 2 (Exposure time: 30 min, 60 min) mixed factorial ANOVAs were run for the SIGH-SAD-SR total score, both of its subscales, the BDI, and the MEQ. Exposure time did not have a significant main effect for any measure (F values ranged between 0.05 and 0.20 with P values between 0.66 and 0.74), nor were any significant interactions found between exposure time and any of the other factors (F values ranged between 0.008 and 2.04 with P values between 0.14 and 0.99). Therefore, to increase statistical power, exposure time was dropped from further analyses.

3.7. Treatment phase and treatment group effects

Table 1 shows descriptive statistics for each of the clinical measures at pretreatment, midtreatment, and posttreatment for the combined HDNI and the combined PLCB groups. At the pretreatment baseline, the groups did not differ significantly in any clinical measure as indicated by independent t-tests: total SIGH-SAD-SR, t (38) = − 0.88, P = 0.39, HAM-D subscale, t (38) = − 0.97, P = 0.34, ATYP subscale, t(38) = − 0.29, P = 0.77, BDI, t (38) = − 1.28, P = 0.18, and MEQ, t (38) = 1.38, P = 0.18.

Table 1
Means and standard errors for the combined HDNI and combined PLCB groups for each clinical measure before testing (Pre), after nine days (Mid) and after 18 days (Post).

	HDNI group			PLCB group		
Measure	Pre	Mid	Post	Pre	Mid	Post
SIGH-SAD-SR	35.1 (2.6)	19.3 (2.6)	13.7 (2.3)	38.0 (2.0)	26.6 (2.7)	21.5 (2.4)
HAM-D subscale	22.6 (2.0)	13.2 (1.9)	9.1 (1.5)	25.0 (1.6)	16.7 (1.7)	13.3 (1.6)
ATYP8 subscale	12.5 (1.0)	6.2 (0.8)	4.6 (1.0)	12.9 (0.9)	9.8 (1.1)	8.2 (1.0)
BDI	25.5 (1.8)	13.4 (2.2)	8.3 (2.0)	28.1 (1.4)	17.7 (2.0)	14.7 (2.1)
MEQ	44.6 (2.9)	44.5 (2.9)	46.2 (2.6)	39.1 (2.7)	40.5 (2.8)	40.1 (2.9)

Note: HDNI = high-density negative ions, PLCB = placebo condition, zero-density negative ions, SIGH-SAD-SR = Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version – Self Rating (Subscales: HAM-D = Hamilton Depression Rating Scale and ATYP8 = Atypical Items); BDI = Beck Depression Inventory; MEQ = Morningness-Eveningness Questionnaire.

Three (Treatment phase: pretreatment, midtreatment, posttreatment) × 2 (Treatment group: HDNI, PLCB) mixed model factorial ANOVAs were conducted for each of the clinical measures. Results are shown in Table 2 and for individual SIGH-SAD-SR scores in Fig. 1. Similar to our previous findings (Flory et al., 2010), significant decreases were found for all four treatment groups across treatment phase for the total SIGH-SAD-SR, the HAM-D subscale, the ATYP8 subscale, and the BDI. Interestingly, MEQ scores did not change over treatment phase (Table 2). Two significant main effects of treatment were found. The HDNI group (M = 22.7, $S.E.$ = 2.00) had significantly lower total SIGH-SAD-SR scores than did the PLCB group (M = 28.7, $S.E.$ = 2.00) as well as having significantly lower ATYP8 subscale scores (HDNI group, M = 7.7, $S.E.$ = 0.76) than did the PLCB group, (M = 10.3, $S.E.$ = 0.76).

Although not statistically different, the pretreatment scores were slightly higher for the combined PLCB group than for the combined HDNI group. We ran 2 (Percent change: pretreatment to midtreatment, pretreatment to posttreatment) × 2 (Treatment group: HDNI, PLCB) mixed model factorial ANOVA to control for pretreatment score. With one exception, results for all the measures were similar to results of the raw score ANOVAs displayed in Table 2. The one difference was a significant interaction between percent change and treatment group for BDI scores, F (1, 38) = 4.10, P = 0.05, η_p^2 = 0.10. Percent improvement increased more steeply between midtreatment and posttreatment for the HDNI group (mean difference of 21.5%) than for the PLCB group (mean difference of 9.7%).

3.8. Clinical response rates

Fig. 1 shows the effectiveness of the treatments as indicated by those subjects in each treatment group meeting either of two clinical response criterion scores for the SIGH-SAD-SR. Criterion 1 required a SIGH-SAD-SR midtreatment or posttreatment score of at least 50% lower than that at pretreatment baseline, and the more strict Criterion 2 required this 50% reduction as well as a HAM-D score of 7 or less and an ATYP8 scores of 7 or less (Terman et al., 1995) at midtreatment or posttreatment. Fig. 2 shows the percentage of subjects in each treatment group meeting either of the two clinical response criteria for the SIGH-SAD-SR. This figure also shows the percentage of subjects in each treatment group with a posttreatment BDI score that was at least 50% lower than that at pretreatment.

A significantly greater percentage of subjects in the combined HDNI group (80%) met Criterion 1 compared to that (35%) of the combined PLCB group, χ^2 (1, N = 40) = 8.29, P = 0.004, φ = 0.46. Similarly, a significantly greater percentage (50%) of subjects in the combined HDNI group met the more stringent Criterion 2 than those (10%) in the combined PLCB group, χ^2 (1, N = 40) = 7.62, P = 0.006, φ = 0.44. For the BDI, significantly more subjects (75%) in the combined HDNI group showed at least a 50% decline from pretreatment levels than did those (40%) in the combined PLCB group, χ^2 (1, N = 40) = 5.01, P = 0.025, φ = 0.35. At baseline, every subject in both groups had a pretreatment BDI score greater than the “minimal depression” cutoff score (9), whereas at posttreatment, 75% of subjects in the combined HDNI group were at or below this cutoff score compared with 30% in the combined PLCB group; this also represents a significant difference χ^2 (1, N = 40) = 6.65, P = 0.01, φ = 0.45.

3.9. MEQ correlations with clinical measures

The pretreatment correlation between MEQ scores and total SIGH-

Table 2
Mixed model factorial ANOVA results for each clinical measure across treatment phase.

Measure	Main effect of treatment phase	η_p^2	Main effect of treatment group	η_p^2	Interaction effect	η_p^2
SIGH-SAD-SR	63.96***	0.63	4.45*	0.10	1.24	0.03
df	(2,76)		(1,38)		(2,76)	
HAM-D subscale	62.21***	0.62	2.78	0.07	0.28	0.01
df[a]	(1.828, 69.471)		(1,38)		(1.828, 69.471)	
ATYP8 subscale	33.63***	0.47	5.84*	0.13	2.79	0.07
df[a]	(1.821, 69.204)		(1, 38)		(1.821, 69.204)	
BDI	86.12***	0.69	3.70	0.09	1.05	0.03
df[a]	(1.804, 68.536)		(1, 38)		(1.804, 68.536)	
MEQ	1.13	0.03	1.81	0.04	0.80	0.02
df[a]	(1.576, 59.905)		(1, 38)		(1.576, 59.905)	

Note: SIGH-SAD-SR = Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version-Self Rating (Subscales: HAM-D = Hamilton Depression Rating Scale and ATYP8 = Atypical Items); BDI = Beck Depression Inventory; MEQ = Morningness-Eveningness Questionnaire; η_p^2 = partial eta squared (effect size).

* $P < 0.05$.

*** $P < 0.001$.

[a] Assumption of sphericity not met; degrees of freedom adjusted by the Huynh-Feldt correction.

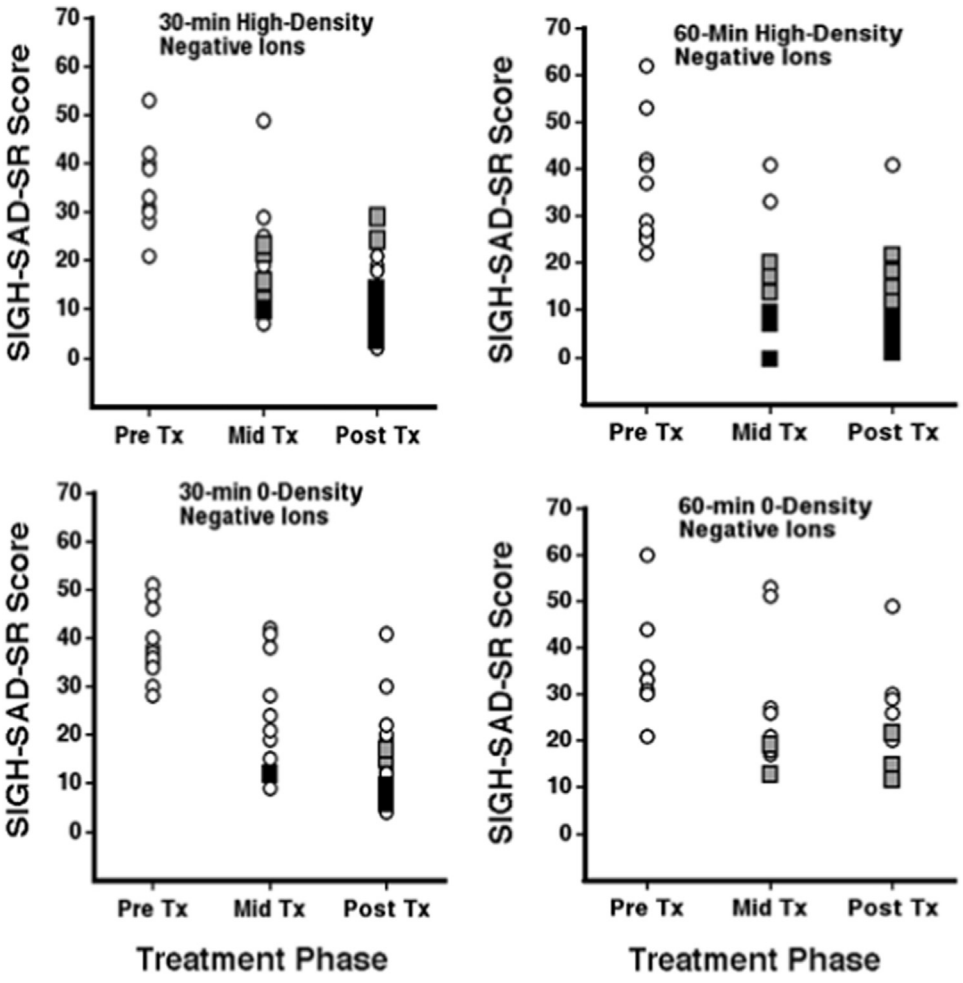

Fig. 1. Scatterplots of each subject's Structured Interview Guide for the Hamilton Depression Inventory-Seasonal Affective Version-Self-Rating (SIGH-SAD-SR) scores prior to treatment (Pre-Tx), midway through treatment sessions (Mid-Tx), and following all treatment sessions (Post-Tx). Open circles indicate those subject's that met neither response Criterion 1: a 50% reduction in SIGH-SAD-SR score from pretreatment to either midtreatment or post-treatment nor response Criterion 2: a 50% reduction in SIGH-SAD-SR score from pretreatment to either midtreatment or posttreatment, a score of 7 points or less on the 21-item Hamilton Depression Rating Subscale of the SIGH-SAD-SR, and a score of 7 points or less on the 8-item Atypical Items Subscale of the SIGH-SAD-SR. Gray squares indicate those subjects that met only response Criterion 1, and black squares indicate those subjects that met response Criterion 2.

SAD-SR scores for all 40 subjects combined was negative and statistically significant, r (38) = − 0.32, P = 0.045. Negative correlations were found between MEQ scores and all clinical measure scores at pretreatment, midtreatment, and posttreatment for both groups (Table 3). Because higher scores on the MEQ reflect more of a morningness orientation, eveningness was associated with greater levels of depression and SAD symptoms than was morningness. Only the combined HDNI group showed an increase in the strength of the correlations over treatment time. At posttreatment, all correlations between MEQ scores and clinical measure scores were significant for the combined HDNI group but not for the combined PLCB group.

4. Discussion

Combined active treatments with high-density negative air ions resulted in significantly greater alleviation of SAD symptoms than did combined placebo conditions, corroborating the findings of previous studies (Terman and Terman, 1995, 2006; Terman et al., 1998). Significant main effects of treatment were found for both total SIGH-SAD-SR scores and ATYP8 subscale scores, with subjects in the combined

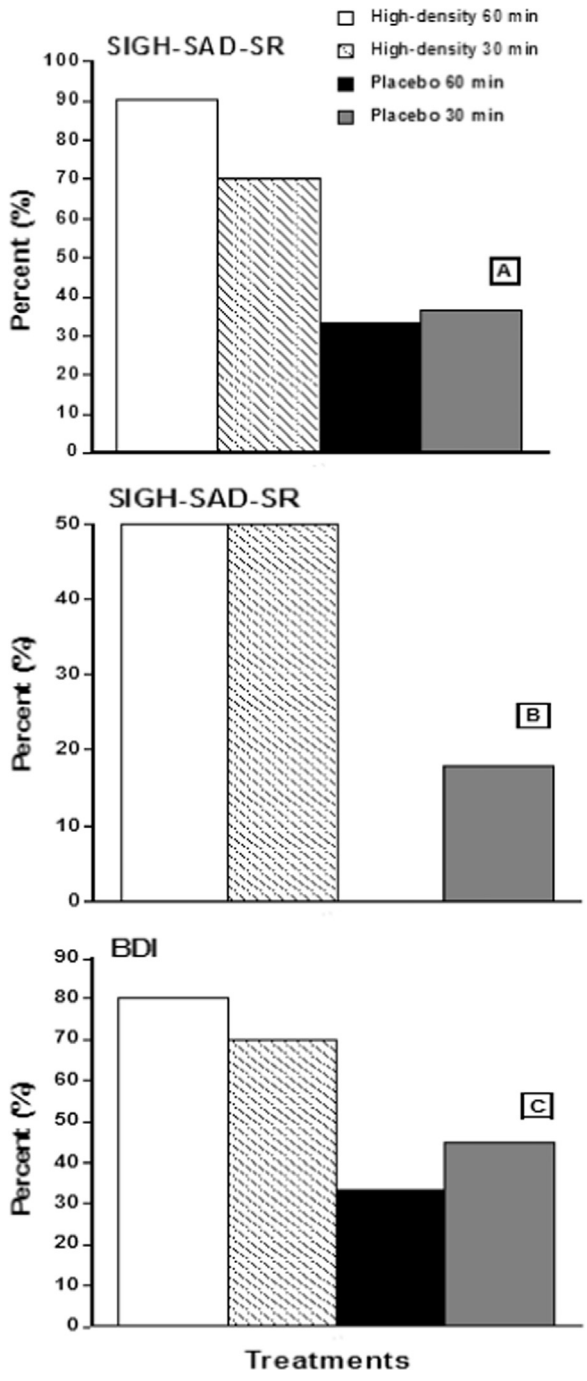

Fig. 2. Percentage of subjects meeting (A) the moderate response criterion of at least a 50% reduction of Structured Interview Guide for the Hamilton Depression Inventory–Seasonal Affective Version–Self Rating (SIGH-SAD-SR) score from pretreatment to posttreatment, (B) the more strict joint response criteria of a 50% or greater reduction of SIGH-SAD-SR score as well as posttreatment scores on the subscales of the SIGH-SAD-SR (21-item Hamilton Depression Rating Subscale [HAM-D] and 8-item Atypical Items Subscale [ATYP8]) of 7 or less, and (C) the moderate response criterion of at least a 50% reduction of Beck Depression Inventory (BDI) score from pretreatment to posttreatment.

HDNI group having significantly lower scores on both measures than did those in the combined PLCB group. The decrease in SIGH-SAD-SR total scores was mostly due to changes in the ATYP8 subscore; HAM-D depression scores showed less relative change in response to the active treatments when compared to the placebo treatments. However, HAM-D depression scores have been shown to significantly decrease in other studies of negative ion effects on SAD (reviewed by Perez et al., 2013). Flory et al. (2010) found only a trend towards significant effects for negative ion exposure, but the number of treatment sessions, 12, was lower in that study compared to the current study with 18 treatment sessions. Similar increases in negative air ion efficacy with increased number of treatment sessions were demonstrated by Terman et al. (1998) for subjects with SAD and by Goel et al. (2005) for subjects with major depressive disorder. Perez at al. (2013) did not report a dose-response between total exposure time and posttreatment depression level when comparing different experiments, but the methods of those studies differed enough (e.g., treatment location, ion concentration) that it is difficult to make direct comparisons; more controlled studies are needed.

The small sample sizes in this study (group *n* ranging from 9 to 11) made assessing exposure time effects problematic. There is some evidence of a potential duration effect in that 90% of the subjects with 60-min exposure to high-density air ions met the moderate response criterion (decrease of 50% or more of SIGH-SAD-SR scores) compared to 70% in the 30-min active group. Replication with a larger sample size would be better able to assess effects of treatment duration. For example, all posttreatment scores were slightly higher, although not statistically different, for the PLCB 30′ group compared to the PLCB 60′ group, most likely due to sampling error. For combined groups, analysis of clinical response criteria showed clear superiority of the HDNI group over the PLCB group for negative ion exposure of at least 30 min. Harmer et al. (2012) found that a single 30 min exposure to HDNI treatment resulted in a reversal of negative emotional processing in individuals with SAD, although this brief exposure had no effect on mood. Goel and Etwaroo (2006) did find decreases in mood/depression in a college sample in as soon as 15 min after brief exposure to negative ions, illustrating that even very short term exposure to negative air ions can have measurable effects.

Similar to previous studies using negative air ion exposure (Terman and Terman, 1995, 2006; Terman et al., 1998), no aversive side effects of exposure to negative air ion treatment were found. In no instance were side effects covering the 17 distinct physical categories measured by the SAFTEE inventory found to be more prevalent in the HDNI groups than in the PLCB groups. In addition, for 16 of the 17 categories, side effects decreased over treatment time, and the decrease was similar for all groups. These findings, along with similar decreases over treatment phase found for all four groups in total SIGH-SAD-SR scores, SIGH-SAD subscale scores, and BDI scores indicate strong placebo effects in this study. Similar placebo effects have been found in previous studies of non-pharmacological treatments for SAD (e.g., Eastman et al., 1998; Flory et al., 2010) and, more generally, in clinical trials of various treatments for major depression (Walsh et al., 2002).

The absence of significant changes in MEQ scores across treatment indicates no evidence of a circadian shift for any treatment group across the duration of the study, unlike the phase-advance shift observed with morning light therapy for SAD (e.g., Terman and Terman, 2010). Similarly, Goel et al. (2005) found subjects with major depressive disorder treated with negative air ions did not show any evidence of a phase advance in circadian rhythm. Wirz-Justice (2009) indicated that light treatment has both a circadian phase shift effect as well as a global drug-like effect, similar to anti-depressant drugs. Negative air ions appear to have this global effect and could be, as is light therapy (e.g., Loving et al., 2002), a good adjunctive treatment with antidepressant drugs. Pairing negative ion treatment with light therapy may be more problematic due to the potential effects of the metal light box on ion dispersion.

Previous studies have found a negative relationship between MEQ scores and non-seasonal depression severity (Chelminski et al., 1999; Drennan et al., 1991) and between MEQ scores and SAD severity (Lee et al., 2011; Murray et al., 2003: Natale et al., 2005; Tonetti et al., 2012). Low scores on the MEQ indicate an eveningness chronotype which is more strongly associated with mood and other mental disorders than is a morningness chronotype (Fares et al., 2015); although

Table 3
Pearson r correlation coefficients between scores on the MEQ (Morningness-Eveningness Questionnaire) and each clinical measure pretreatment, midtreatment, and posttreatment by combined treatment group.

Clinical measure	HDNI group (n = 20)	PLCB group (n = 20)
Total SIGH SAD-SR		
Pretreatment	− 0.16	− 0.48*
Midtreatment	− 0.51*	− 0.48*
Posttreatment	− 0.74***	− 0.30
HAM-D subscale		
Pretreatment	− 0.20	− 0.32
Midtreatment	− 0.39	− 0.40
Posttreatment	− 0.66**	− 0.35
ATYP8 subscale		
Pretreatment	− 0.02	− 0.50*
Midtreatment	− 0.69**	− 0.54*
Posttreatment	− 0.71***	− 0.16
BDI		
Pretreatment	− 0.37	− 0.14
Midtreatment	− 0.61**	− 0.25
Posttreatment	− 0.72***	− 0.21

Note: HDNI = high-density negative ions; PLCB = placebo, zero-density negative ions; SIGH-SAD-SR = Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version – Self Rating (Subscales: HAM-D = Hamilton Depression Rating Scale and ATYP8 = Atypical Items); BDI = Beck Depression Inventory.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

not all studies have reported a strong association between the two (e.g., Merikanto et al., 2016). In the present study, all correlations between MEQ scores and the clinical measures were negative, indicating that those who scored low on the MEQ (eveningness chronotypes) had higher SAD scores (Table 3).

In the HDNI group, the strength of the correlations between MEQ scores and clinical measures unexpectedly increased over treatment phase; a pattern not seen in the PLCB group. Thus, it appears that treatment with negative air ions was more effective for participants with more of a morningness chronotype than for those with an eveningness chronotype. Similar to our results, Corruble et al. (2014) found that having a morningness chronotype predicted a positive response to agomelatine, a melotonergic antidepressant, and Goel et al. (2005) found that those with a delayed melatonin onset phase, indicating a more eveningness chronotype, showed decreased responsiveness to light treatment for major depressive disorder. As it was not a variable in our initial research design, we were not able to determine whether low-MEQ subjects are selective non-responders to negative ion treatment, but this is an important question to be addressed in future research. Assessing chronotype in clinical trials for depression treatments in general may help explain individual differences in treatment responsiveness.

Limitations of this study involved the testing environment and characteristics of the sample. Although assessment in a laboratory setting allowed direct measurement of negative ion and ozone levels, this artificial setting did not represent how negative ion generators typically would be used in a home environment; however, our findings when taken in conjunction with those studies with greater ecological validity (Terman and Terman, 1995, 2006; Terman et al., 1998) help establish that negative ion exposure is an effective treatment for SAD both in laboratory and natural settings. Sample sizes were small, limiting statistical power, and were non-representative of the general population; the subjects were primarily young adult females, the demographic most susceptible to SAD (Magnusson, 2000).

In conclusion, our results corroborate the findings of previous studies that exposure to negative air ions is an effective method to alleviate symptoms of SAD. Unlike most previous studies, ours was conducted under controlled laboratory conditions, and we were able to directly measure negative ion levels and to detect no increase in ozone production during treatment. We also showed that treatment with negative air ions was not associated with any negative side effects when compared to the placebo treatment. Thus, we have established that a relatively brief daily exposure to negative air ions is an effective and safe treatment for seasonal affective disorder; in addition, the effect of negative air ions may be reduced in people with eveningness chronotypes.

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