

Treatment of Seasonal Affective Disorder with a High-Output Negative Ionizer

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ABSTRACT

This study was designed to evaluate the antidepressant effect of negative ions in the ambient air as a potential treatment modality for seasonal affective disorder. Twenty-five subjects with winter depression underwent a double-blind controlled trial of negative ions at two exposure densities, 1×10^4 ions/cm³ or 2.7×10^6 ions/cm³, using an electronic negative ion generator with wire corona emitters. Home treatments were taken in the early morning for 30 min over 20 days, followed by withdrawals.

The severity of depressive symptoms (prominently including the reverse neurovegetative symptoms of hypersomnia, hyperphagia, and fatigability) decreased selectively for the group receiving high-density treatment. Standard depression rating scale assessments were corroborated by clinical impressions. When a remission criterion of 50% or greater reduction in symptom frequency/severity was used, 58% of subjects responded to high-density treatment while 15% responded to low-density treatment ($\chi^2 = 5.00$, $df = 1$, $p = 0.025$). There were no side effects attributable to the treatment, and all subjects who responded showed subsequent relapse during withdrawal.

Treatment with a high-density negative ionizer appears to act as a specific antidepressant for patients with seasonal affective disorder. The method may be useful as an alternative or supplement to light therapy and medications.

INTRODUCTION

Most treatment studies of seasonal affective disorder (SAD) (Rosenthal et al., 1984) have used bright light presented in morning, evening, or both, with generally strong results exceeding those with use of dim or brief light controls (Terman et al., 1989; Terman et al., 1990). There have been only a few controlled drug studies of SAD, focusing on specific serotonin reuptake inhibitors (d-fenfluramine (O'Rourke et al., 1989), fluoxe-

tine (Lam et al., 1994) and a monoamine oxidase inhibitor (moclobemide [Lingjaerde et al., 1993]) with apparent benefits over placebo. The present study investigated a different class of somatic treatment, negative ions, as diffused into the air by an electronic device using corona discharge.

Little is known about the route of ingestion of negative ions or their mechanism of action on central nervous system activity. Indeed, the very bioactivity of negative ions is controversial (Bailey 1987), and double-blind placebo

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controlled trials and systematic dose-response studies are largely lacking. In a critical review of the literature, Charry (1987) concluded that "(1) there appear to be effects of ions on biological and behavioral responses in both animals and humans; (2) when these effects occur, they are for the most part small in absolute magnitude; and (3) the effects that have been observed are for the most part transient" (p. 146). Nonetheless, the popular literature (e.g., Soyka 1977) has persistently reported salutary effects of negative ion exposure on human ailments (such as fatigability, irritability, sleep disturbance, and infectious diseases) and has attributed symptom exacerbation to positive ion exposure, which might vary geographically, seasonally, with the weather, and in deficient indoor environments.

There is a long but controversial history of animal and human experiments suggesting various effects of positive and negative ion exposure on central nervous system and peripheral serotonin activity (Charry 1987). Brain serotonin levels are known to decrease in the fall and winter (Carlsson et al., 1980), and there is a seasonal rhythmicity of serotonin in blood platelets (Wirz-Justice and Richter 1979). Indeed, serotonergic mediation of the antidepressant response in SAD has been hypothesized (Jacobsen 1989), as exemplified by behavioral activation and mood elevation following infusion of the serotonin agonist *m*-chlorophenylpiperazine (Joseph-Vanderpool et al., 1993).

Eastman et al. (1993) took advantage of the plausibility of an antidepressant effect of negative ions in designing a placebo control for light therapy of winter depression. The fact that negative ions are not directly perceptible by sensory transduction served to make the control credible to the subjects, who were treated with a *deactivated* negative ion generator or bright light. Thus, the placebo was inert, and subjects were told that the ionizer might or might not be activated. Initial results of the study (still in progress) indicate similar clinical responses to the deactivated ion generator and light, which raises the question of a strong placebo component in light treatment. The study did not assess clinical responses using an

activated ion generator. By contrast, the present study compared actual negative ion treatment at two dose levels.

MATERIALS AND METHODS

Subjects

Twenty-five subjects were diagnosed with seasonal affective disorder by the criteria of Rosenthal et al. (1984) and the *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)* (American Psychiatric Association 1987) criteria for major depressive disorder, recurrent ($n = 15$), or bipolar disorder not otherwise specified ($n = 10$), both with seasonal pattern. They were entered into treatment after a minimum 2 week baseline of depressed mood in late fall or winter. All were asymptomatic in spring and summer, and showed no other *DSM-III-R* axis I disorder or potentially complicating medical illness. The group included 22 women and 3 men, age 38.2 ± 11.0 years (mean \pm SD), who had no prior experience with light or negative ion treatment and were not taking psychotropic medication. (The imbalance of sexes reflects the large preponderance of females among patients seeking treatment for SAD.) Criteria for entry were a score of at least 20 points using the Structured Interview Guide for the Hamilton Depression Rating Scale, SAD version (SIGH-SAD) (Williams et al., 1992), including a score of at least 10 on the basic Hamilton Depression Rating Scale (HAM-D, 21 items) and a score of at least 5 on a supplementary scale of atypical symptoms (ATYP, 8 items) (Terman et al., 1990). Atypical symptoms included hypersomnia, hyperphagia, fatigability, and associated reverse neurovegetative symptoms characteristic of SAD, which contrast with the classic symptoms of major depressive disorder with melancholic features (American Psychiatric Association 1987).

Apparatus

Negative ions were produced by an apparatus providing ion densities of approximately

1×10^4 ions/cm³ or 2.7×10^6 ions/cm³ (Sea-King AB, Västerås, Sweden). The unit measured 16 cm \times 7.5 cm \times 6 cm and weighed 435 g. It was set on a tubular plastic floor stand 100 cm from the floor, with three wire corona ion emitters facing the seated subject at a distance of approximately 92 cm. Subjects were loaned the apparatus for use at home, and were instructed to place it at least 92 cm from walls, and away from electrical devices, grounded surfaces, and ventilation ducts. Windows and doors were kept closed during treatment sessions.

Procedure

Subjects were randomly assigned to low ($n = 13$) or high ($n = 12$) ion density conditions. (Other subjects were simultaneously randomized into bright light conditions, not reported here). The informed consent described the study as comparing two potentially effective treatment doses, and did not refer to low-density ions as a placebo. Before treatment, but after demonstration of the apparatus, subjects completed a questionnaire that gauged their expectations for positive treatment response on a scale of 1 to 5 (1, no improvement; 2, minor improvement; 3, moderate improvement; 4, major improvement; 5, complete remission). At both baseline and posttreatment evaluations they completed a comprehensive 96-item checklist for side effects based on a standard structured interview (SAFTEE) (National Institute of Mental Health 1986) categorized according to organ system or body part (e.g., head, eyes/vision, ears/hearing, mouth, chest, heart, stomach). Symptoms were rated on a frequency/severity scale of 1 to 5 (1, not at all; 2, a little bit; 3, moderate; 4, quite a bit; 5, extreme). Treatment was administered for 20 days in 30 min sessions shortly after arising between 5:30 and 8:30 a.m., and was followed by a withdrawal of 7–14 days. Subjects maintained daily ratings of sleep times and mood, and compliance was monitored by daily telephone messages noting the time of treatment. Interview raters who had no knowledge of the treatment condition administered clinical evaluations, using the

SIGH-SAD and Clinical Global Impressions (CGI) (Guy 1976) scales, at baseline, after 10 and 20 days of treatment, and at the end of withdrawal.

RESULTS

A two-way repeated measures ANOVA on SIGH-SAD scores after 10 and 20 days of treatment showed a significant group effect ($F = 4.706$, $df = 1$, $p = 0.041$), with high-density treatment producing lower scores (i.e., fewer symptoms). There was no significant time effect or group \times time interaction, nor were group differences significant at baseline or after withdrawal (two-tailed t -tests).

The finding of a statistically significant group contrast in clinical response was further analyzed in terms of the magnitude of differences—expressed as effect size (normalized difference between means)—on the two component subscales of the SIGH-SAD (HAM-D and ATYP). By convention, an effect size (d) of 0.2 is considered small; 0.5, moderate; and 0.8, large (Cohen 1988). Although statistical significance can be obtained with small effect size, the clinical importance of such a result might be questioned. As illustrated in Figure 1, the classic depressive symptoms of the HAM-D showed only small relative benefit of high-density ions at 10 days ($d = 0.25$), but moderate benefit at 20 days ($d = 0.61$). The result was more pronounced for the atypical symptoms, with a moderate effect at 10 days ($d = 0.66$) and a large effect at 20 days ($d = 0.96$). Treatment scores for the low-density group remained within the depressed range, and there was close convergence of withdrawal scores for the two groups, indicative of relapse following termination of high-density treatment.

Although consideration of raw scale scores, as above, serves to identify group differences, it does not clearly demonstrate clinical success rate. For that purpose, we estimated the frequency of clinical remissions after 20 days of treatment by using a set of discrete improvement criteria (SIGH-SAD score at least 50% lower than that at baseline, HAM-D and ATYP scores each 7 points or below [within the nor-

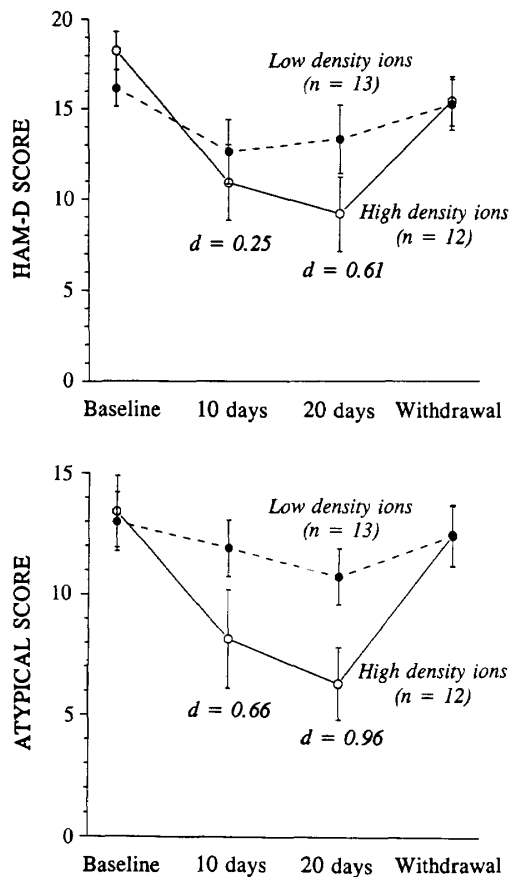


FIG. 1. Depression rating scale scores (mean \pm SEM) across phases of the experiment. Top, Hamilton Depression Rating Scale (HAM-D). Bottom, supplementary scale of reverse neurovegetative (atypical) symptoms. *d*, effect size (normalized difference between means).

mal range], and CGI-Improvement ratings of 1 or 2 [1, very much improved; 2, much improved]). As shown in Table 1, 58% of subjects

achieved remissions under high-density treatment using a SIGH-SAD score reduction of at least half as the criterion. Remission rates declined for both low- and high-density groups as the clinical criteria were made stricter. Nonetheless, high-density response was always superior to low-density response, and the size of effect of proportions (*h*) (Cohen 1988) increased with stricter criteria to a maximum of *h* = 1.41 (very large) when all three criteria were jointly applied.

Apart from symptoms directly related to depression, the SAFTEE side-effect checklist indicated a scatter of mild somatic symptoms (score of 2) at the posttreatment assessment that did not differ between low- and high-density ion groups or indicate emergence relative to the pretreatment baseline. Within the high-density group, moderate severity (scores of 3 or 4) was reported by two (16.67%) or three (25%) subjects for a discrete set of gastrointestinal symptoms (abdominal discomfort, diarrhea, gas), peripheral symptoms (sore throat, nasal congestion, eye irritation), pain (muscle, bone, joint), and fever. These were all associated with winter colds and viral infections, and did not differ systematically from reports at baseline, or reports by the low-density ion group. No severe symptoms (score of 5) were reported except for one case of flu-associated fever and muscle pain in a subject who received low-density ions.

Although subjects were not randomized into the low- and high-density treatment groups according to age, and mean ages of the two groups differed significantly (low, 42.62 ± 21.59 yr; high, 33.58 ± 8.43 yr; *p* = 0.03 by two-tailed *t*-test), the percentage of improvement in SIGH-SAD scores at the 20-day assessment was not correlated with age (*r* = -0.01).

TABLE 1. CLINICAL REMISSION RATES (%) ACCORDING TO PROGRESSIVELY STRICT CRITERIA

SIGH-SAD red. \geq 50%			SIGH-SAD red. \geq 50% HAM-D \leq 7, ATYP \leq 7			SIGH-SAD red. \geq 50% HAM-D \leq 7, ATYP \leq 7 CGI (I) \leq 2		
High ^a	Low ^b	ES (h) ^c	High	Low	ES (h)	High	Low	ES (h)
58	15	0.94	50	8	1.00	42	0	1.41

^aIon density, 2.7×10^6 ions/cm³.

^bIon density, 1×10^4 ions/cm³.

^cEffect size of proportions.

Pretreatment expectation ratings tended to be moderately positive and did not differ between the low- and high-density ion groups (3.00 ± 1.08 and 3.00 ± 1.04 , respectively). Several subjects in the high-density group spontaneously reported surprise that they had responded, contrary to their expectations. Indeed, expectation ratings were not positively correlated with percentage improvement in SIGH-SAD scores ($r = -0.51$, NS), which further suggests that clinical improvement resulted from the treatment manipulation—whether negative ions per se or physical byproducts such as oxidant gases (see Discussion)—and not subject bias.

DISCUSSION

Exposure to the high-density negative ion generator appears to be specifically antidepressant in patients with SAD. The response to the low-density condition (15% of subjects, as defined by a SIGH-SAD score reduction of at least half) can be regarded as a placebo rate. It should be noted that ion density in the range of 10^4 ions/cm³ has been defined as a medium, not low, dose in prior biological research (Charry 1987). The response to the high-density condition (58%) leaves room for further improvement, which might be achieved by dosing manipulations. Although ion density in the range of 10^6 ions/cm³ is greater than that used in most prior research, the 30 min daily exposure duration is brief. However, response rates in the range of 60% are typical also of antidepressant medications (Klein et al., 1980), and the present result is approximately equivalent. Furthermore, data indicate that the high-density response does not differ statistically significantly from that found for morning light treatment at 10,000 lux for 30 min (Terman and Terman 1994). A definitive comparison awaits completion of expanded trials in progress.

The mechanism of action of the antidepressant effect is unknown, and an ion-related serotonergic response should not be presumed pending further investigation of the physical stimulus and its physiological effects. The production of negative ions by electronic devices such as we used can simultaneously generate

DC electrical fields and oxidant gases, notably ozone (Klavet 1987). The precipitation of airborne pollutants from circulation may also have indirect salutary effects. Uncontrolled variables such as room size, humidity, weather conditions, ambient positive ion concentrations, proximity of grounded devices and even clothing and furniture fabrics may affect local negative ion concentration, and thus introduce dose variability in normal home use, which could render the treatment ineffective in individual cases and blur between-group differences in dose-response studies. The success of our high-density condition may have depended on the high electron flow rate of the generator, 45×10^{12} /s (which far exceeds that of common commercial units), overriding uncontrolled environmental factors that may act to reduce ion availability.

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REFERENCES

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd ed., rev. Washington, D.C.: American Psychiatric Association, 1987.
- Bailey WH. Biological responses to air ions: Is there a role for serotonin? In: Charry JM, Kavet R, eds. Air ions: Physical and biological aspects. Boca Raton, FL: CRC Press, 1987, p 151-160.
- Carlsson A, Svennerholm L, Winblad B. Seasonal and circadian monoamine variations in human brains examined post-mortem. *Acta Psychiatr Scand* 1980;61: 75-85.
- Charry JM. Biological effects of air ions: A comprehensive review of laboratory and clinical effects. In: Charry JM, Kavet R, eds. Air ions: Physical and biological aspects. Boca Raton, FL: CRC Press, 1987, p 91-150.
- Cohen J. Statistical power analysis for the behavioral sciences, 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.

- Eastman CI, Young MA, Fogg LF. A comparison of two different placebo-controlled SAD light treatment studies. In: Wetterberg L, ed. *Light and biological rhythms in man*. Oxford: Pergamon, 1993, p 371-383.
- Guy W. ECDEU assessment manual for psychopharmacology, rev. ed. DHEW Publication No. (ADM) 76-338. Washington, D.C.: U.S. Government Printing Office, 1976.
- Jacobsen FM, Murphy DL, Rosenthal NE. The role of serotonin in seasonal affective disorder and the antidepressant response to phototherapy. In: Rosenthal NE, Blehar MC, eds. *Seasonal affective disorders and phototherapy*. New York: Guilford, 1989, p 333-341.
- Joseph-Vanderpool JR, Jacobsen FM, Murphy DL, Hill JL, Rosenthal NE. Seasonal variation in behavioral responses to *m*-CPP in patients with seasonal affective disorder and controls. *Biol Psychiatry* 1993;33:496-504.
- Klavet R. Hypothetical neural substrates for biological responses to air ions. In: Charry JM, Kavet R, eds. *Air ions: Physical and biological aspects*. Boca Raton, FL: CRC Press, 1987, p 162-180.
- Klein DF, Gittleman R, Quitkin FM, Rifkin A. Diagnosis and drug treatment of psychiatric disorders. Baltimore: Williams and Wilkins, 1980.
- Lam RW, Gorman C, Michalon M, Steiner M, Levitt AJ. A multicentre, placebo-controlled study of fluoxetine in seasonal affective disorder. *Soc Light Treatment Biol Rhythms Abst* 1994, 6:5.
- Lingjaerde O, Reichborn-Kjennerud T, Haggag A, Gärtner I, Narud K, Berg EM. Treatment of winter depression in Norway. II. A comparison of the selective monoamine oxidase A inhibitor moclobemide and placebo. *Acta Psychiatr Scand* 1993;88:372-380.
- National Institute of Mental Health. Systematic assessment for treatment emergent effects (SAFTEE). Rockville, MD: National Institute of Mental Health, 1986.
- O'Rourke D, Wurtman JJ, Wurtman RJ, Chebli T, Gleason R. Treatment of seasonal depression with d-fenfluramine. *J Clin Psychiatry* 1989;50:343-347.
- Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y, Mueller PS, Newsome DA, Wehr TA. Seasonal affective disorder: A description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry* 1984;41:72-80.
- Soyka F. *The ion effect*. New York: Bantam, 1977.
- Terman M, Terman JS, Quitkin FM, McGrath PJ, Stewart JW, Rafferty B. Light therapy for seasonal affective disorder: a review of efficacy. *Neuropsychopharmacology* 1989;2:1-22.
- Terman JS, Terman M, Schlager D, Rafferty B, Rosofsky M, Link M, Gallin PF, Quitkin FM. Efficacy of brief, intense light exposure for treatment of winter depression. *Psychopharm Bull* 1990;26:3-11.
- Terman M, Terman JS, Rafferty B. Experimental design and measures of success in the treatment of winter depression by bright light. *Psychopharmacol Bull* 1990; 26:505-510.
- Terman M, Terman JS. A controlled trial of light therapy and negative ions. *Soc Light Treatment Biol Rhythms Abst*. 1994;6:6.
- Williams JBW, Link M, Rosenthal NE, Amira L, Terman M. Structured interview guide for the Hamilton Depression Rating Scale—seasonal affective disorder version (SIGH-SAD), rev. ed. New York: New York State Psychiatric Institute, 1992.
- Wirz-Justice A, Richter R. Seasonality in biochemical determinations: A source of variance and a clue to the temporal incidence of affective illness. *Psychiatr Res* 1979;1:53-60.

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