



Commentary - October 1998

Beginning to See the Light

Light is the first treatment in psychiatry to evolve directly out of modern neuroscience. Yet paradoxically, the biological psychiatry establishment has regarded light therapy with a certain disdain and relegated it to the edge of the journal, not respectable enough, a bit too Californian-alternative, a bit too media overexposed, merely a placebo response by mildly neurotic middle-aged women who don't like nasty drugs.

But light is as effective as antidepressants in some studies, and provides the best evidence to date for the treatment of seasonal affective disorder (SAD) [1-3]. Placebo response rates are high in antidepressant trials, but not in light therapy. "blindness" is a moral imperative in antidepressant trials, but not in light therapy. The advantage of antidepressants over placebo in controlled trials is that multicenter studies can answer questions of relevance [4,6,7]. The single centers in large, controlled, blind trials are able to show that light therapy works better than a convincing placebo is therefore extremely important.

The idea of light therapy came from research on circadian rhythms, where changes in sleep, eating behavior, and weight, for example, are exquisitely timed, for each species, to day length at the latitude inhabited [8]. The circadian pacemaker in the suprachiasmatic nuclei acts as a "clock for all seasons": the window of opportunity for seasonal change is dependent on prior photoperiod [9]. Humans too have retinal melatonin receptors, but these are mostly masked by splendid isolation in living conditions that are manipulated at will. Indeed, such "unnatural" behavior may be the cause of the mood decline in vulnerable individuals.

Beginning to See the Light Archives of General Psychiatry Anna Wirz-Justice, PhD

In the 15 years since the pioneer National Institute of Mental Health study describing SAD and its treatment by bright light [11], a remarkable research interest has developed worldwide, not only in the dark northern fastnesses of Alaska, Canada, Scandinavia, and Siberia, but also in India, Italy, Japan, and the inverse winter of the southern hemisphere. Light therapy is widely used, in spite of the skepticism of colleagues who do not "believe" in a syndrome they have never seen (only about 10% of patients with SAD have ever been hospitalized [8]). Since many study patients are recruited via newspaper advertisements, these psychiatrists consider them merely high placebo responders. The new evidence indicates that they are not.

New York, NY, at 41°N, Chicago, Ill, at 42°N, and Portland, Ore, at 45°N: these 3 articles [1-3] with the largest numbers so far in individual studies, scan the United States from east to west at around the same northerly latitude. In spite of the differences in design, some important correspondences emerge with respect to remission rates (Table).

The 2 placebo-controlled trials [1,2] (what a very cunning idea that negative-ion generator was!) have nearly identical results: both morning and evening light are better than placebo, and morning light is superior to evening light. The third study [3] also demonstrates a morning light superiority but has overall lower improvement rates. In emphasizing the similarities—and not dissecting out why certain differences are found between these populations, or in European studies [12,13]—we have to be cognizant that these comparisons of therapeutic outcome are based on very stringent criteria for remission, not just response, within a rather short time (2-4 weeks). Such stringent criteria, when applied to a 5-week multicenter trial of fluoxetine in patients with SAD, did not differentiate between drug (33%, n=36) and placebo (28%, n=32) [14]. Patients with SAD treated with light for 5 weeks tended to remit more (50%, n=20) than those treated with fluoxetine (25%, n=20; P=.10) [15].

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Light is the first treatment in psychiatry to evolve directly out of modern neuroscience. Yet paradoxically, the biological psychiatry establishment has regarded light therapy with a certain disdain and relegated it to the edge of the paradigm—not molecular enough, a bit too Californian-alternative, a bit too media overexposed, merely a placebo response by mildly neurotic middle-aged women who don't like nasty drugs.

But light is as effective as drugs, perhaps more so. Three articles in this issue provide the best evidence to date that light is an effective antidepressant in seasonal affective disorder (SAD).^[1-3] Placebo response^[4] and nonspecific factors^[5] are an issue in all clinical trials: for light therapy, "blindness" is not simply an oxymoron. Many psychiatrists are unaware that the advantage of antidepressant drugs over placebo in controlled trials is so small that only multicenter studies can answer questions of relevance.^[4,6,7] That 2 single centers^[1,2] in large, controlled, blind trials are able to show that light therapy works better than a convincing placebo is therefore extremely important.

The idea of light therapy came from research into mammalian seasonality, where changes in sleep, eating behavior, and weight, for example, are exquisitely tuned, for each species, to day length at the latitude inhabited.^[8] The circadian pacemaker in the suprachiasmatic nuclei acts as a "clock for all seasons": the window of responsiveness to light at dawn and dusk is dependent on prior photoperiod.^[9] Humans too have retained their intrinsic seasonal responses,^[10] though these are mostly masked by splendid isolation in living boxes where lighting and temperature are manipulated at will. Indeed, such "unnatural" behavior may be one of the factors precipitating seasonal mood decline in vulnerable individuals.

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The Society for Light Treatment and Biological Rhythms (www.websciences.org/sltbr/) has played an important role in the last decade to establish guidelines, standards, and consensus statements for light

therapy. Light is now recommended as the treatment of choice for SAD.[16,17] However, in spite of international recognition, only in Switzerland has the additional economic argument that light is cheaper than drugs attained government endorsement and mandatory reimbursement by medical insurance. In addition to SAD, new applications for light have recently been summarized in the Society for Light Treatment and Biological Rhythms Task Force commissioned by the American Sleep Disorders Association: for circadian-related sleep disorders, aging and Alzheimer's disease, jet lag, and shift work.[18]

But few psychiatrists have yet recognized that light therapy should be considered a mainstream antidepressant modality. Seasonality of depression can also overlap other diagnoses, such as chronic and intermittent depressions, rapid brief depression, dysthymia, bulimia, premenstrual dysphoric disorder, etc. Long-term follow-up documentation indicates that whereas some patients may flip in and out of modes, most remain seasonally susceptible.[19] There is intriguing preliminary evidence for light treatment beyond SAD.[20] Kripke has carried out a systematic comparison of light and antidepressant drug studies in nonseasonal major depression.[7] He argues that we should routinely prescribe light for nonseasonal depression[7]—at least as a drug adjuvant—even before waiting for results from large multicenter trials (which may not even begin, since there is no industrial interest in them).

We need to separate 2 issues: clinical efficacy of light vs mechanisms of action. These clinical trials[1-3] clearly support the claim that light is antidepressant, rather than elucidating how it works. Interpretation of the available data requires multiple levels of explanation. Light targets a neuroanatomical region (the circadian clock), and the SAD literature provides experimental support for both the "phase-shift hypothesis" and the "too-few-photons hypothesis," rather than the original "photoperiod hypothesis." Circadian and serotonergic hypotheses of the pathophysiological mechanisms of SAD are not incompatible: light also acts on a neurochemical substrate within that clock, the serotonergic input from the median raphe. Here we need further research to tease out mechanisms.

The evidence is in that light is an active neurobiological agent. But light therapy has little chance to be widely and properly used for a variety of ills, as long as it appears to the policymakers and grant-givers to lie uncomfortably between pharmaceutical company neglect (for obvious reasons) and the molecular reductionism of academe. These attitudes strikingly contrast with patients' acceptance of light therapy. Light therapy is easy to administer in outpatient settings, lacks major side effects, and, importantly, is cost-effective. Whatever its mode of action, it demands inclusion in the antidepressant armamentarium, now.

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References

1. Terman M, Terman JS, Ross DC. A controlled trial of timed bright light and negative air ionization for treatment of winter depression. *Arch Gen Psychiatry*. 1998;55:875-882.
2. Eastman CI, Young MA, Fogg LF, Liu L, Meaden PM. Bright light treatment of winter depression: a placebo-controlled trial. *Arch Gen Psychiatry*. 1998;55:883-889.
3. Lewy AJ, Bauer VK, Cutler NL, Sack RL, Ahmed S, Thomas KH, Blood ML, Latham Jackson JM. Morning vs evening light treatment of patients with winter depression. *Arch Gen Psychiatry*. 1998;55:890-896.
4. Healy D. Commentary: meta-analysis of trials comparing antidepressants with active placebos. *Br J Psychiatry*. 1998;172:232-234.

5. Joyce CRB. Non-specific aspects of treatment from the point of view of a clinical pharmacologist. In: Shepherd M, Sartorius N, eds. *Non-Specific Aspects of Treatment*. Toronto, Ontario: Huber; 1989:57-94.
6. Elkin I, Shea T, Watkins JT, Imber SD, Sotsky SM, Collins JF, Glass DR, Pilkonis PA, Leber WR, Docherty JP, Fiester SJ, Parloff MB. National Institute of Mental Health Treatment of Depression Collaborative Research Program: general effectiveness of treatments. *Arch Gen Psychiatry*. 1989;46:971-982.
7. Kripke DF. Light treatment for nonseasonal depression: speed, efficacy, and combined treatment. *J Affect Disord*. 1998;49:109-117.
8. Rosenthal NE, Blehar MC, eds. *Seasonal Affective Disorder and Phototherapy*. New York, NY: Guilford Press; 1989.
9. Sumova A, Travnibckova Z, Peters R, Schwartz WJ, Illnerova H. The rat suprachiasmatic nucleus is a clock for all seasons. *Proc Natl Acad Sci U S A*. 1995;92:7754-7758.
10. Wehr TA, Moul DE, Barbato G, Giesen HA, Seidel JA, Barker C, Bender C. Conservation of photoperiod-responsive mechanisms in human beings. *Am J Physiol*. 1993;265:R846-R857.
11. 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.
12. Wirz-Justice A, Graw P, Kraeuchi K, Gisin B, Jochum A, Arendt J, Fisch H-U, Buddeberg C, Poeldinger W. Light therapy in seasonal affective disorder is independent of time of day or circadian phase. *Arch Gen Psychiatry*. 1993;50:929-937.
13. Thalen BE, Kjellman BF, Morkrid L, Wibom R, Wetterberg L. Light treatment in seasonal and nonseasonal depression. *Acta Psychiatr Scand*. 1995;91:352-360.
14. Lam RW, Gorman CP, Michalon M, Steiner M, Levitt AJ, Corral MR, Watson GD, Morehouse RL, Tam W, Joffe RT. Multicenter, placebo-controlled study of fluoxetine in seasonal affective disorder. *Am J Psychiatry*. 1995;152:1765-1770.
15. Ruhrmann S, Kasper S, Hawellek B, Martinez B, Hoeflich G, Nickelsen T, Moeller H-J. Effects of fluoxetine versus bright light in the treatment of seasonal affective disorder. *Psychol Med*. 1998;28:923-933.
16. Depression Guideline Panel. *Depression in Primary Care: Volume 2. Treatment of Major Depression*. Washington, DC: Agency for Health Care Policy and Research, Dept of Health and Human Services; 1993. Publication 93-0551.
17. Rosenthal NE. Diagnosis and treatment of seasonal affective disorder. *JAMA*. 1993;270:2717-2720.
18. Terman M, Boulos Z, Campbell SS, Dijk D-J, Eastman CI, Lewy AJ. Light treatment for sleep disorders: ASDA/SLTBR Joint Task Force Report. *J Biol Rhythms*. 1995;10:101-176.
19. Leonhardt G, Wirz-Justice A, Kraeuchi K, Graw P, Wunder D, Haug H-J. Long-term follow-up of depression in seasonal affective disorder. *Compr Psychiatry*. 1994;35:457-464.
20. Lam R, ed. *Seasonal Affective Disorder and Beyond: Light Treatment for SAD and Non-SAD Conditions*. Washington, DC: American Psychiatric Press; 1998.
(*Arch Gen Psychiatry*. 1998;55:861-862)