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Research report

Light treatment for nonseasonal depression: speed, efficacy, and combined treatment[1]

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Abstract

Background: Using bright light for treating major depressive disorders which are not seasonal needs reassessment. *Methods*: Clinical trials of light treatment for nonseasonal major depressive disorders were compared with selected trials of light treatment of winter depression and with antidepressant clinical drug trials. *Results*: Light treatment of nonseasonal depression produces net benefits in the range of 12–35%, often within 1 week. *Conclusions*: Light's value for nonseasonal and seasonal depression are comparable. Light appears to produce faster antidepressant benefits than psychopharmacologic treatment. *Limitations*: Direct randomizing comparisons between light and medications for nonseasonal depression are not available. *Clinical relevance*: Bright light can be combined with standard therapies for treating nonseasonal depressions and appears synergistic. © 1998 Elsevier Science B.V.

Keywords: Light; Antidepressant; Depression; Clinical trials

1. Introduction

Bright light treatment for winter depression is recognized in the Clinical Practice Guidelines issued by the U.S. Department of Health and Human Services (Depression Guideline Panel, 1993). The American Psychiatric Association's *Treatment of Psychiatric Disorders* also endorsed bright light treatment (Rosenthal, 1995), but failed to note much recent evidence for light's usefulness in nonseasonal depression, so a reassessment of the literature is needed. Partly because the specificity of light treatment for winter depression had been exaggerated, for some time, the literature has been burdened by the notion that bright light treatment in nonseasonal depression lacked benefits similar to those in seasonal depressions (Seasonal Affective Disorder or SAD). The SAD patients with the best responses to bright light have had rather mild depression ratings

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and a tendency to improve with placebo alone (Terman et al., 1989). For example, in a study comparing SAD patients (whose episode duration must have been less than 6 months) with atypical depressives with a mean episode duration of 142 months (Stewart et al., 1990), one would have anticipated that the patients with briefer illnesses would demonstrate more spontaneous remission even before factoring in the effects of light treatment. Winter depressions are only a small portion of the depressive illnesses in the population, with a history of seasonal remission and mild severity which might suggest a particularly favorable prognosis. The few studies which have attempted to compare the light responsiveness of seasonal and nonseasonal depressives have not yet critically balanced factors of severity, duration, recruitment bias, and expectation.

Pilot controlled trials of bright light for treatment of nonseasonal depression began somewhat before the excitement over winter depression developed (Kripke, 1981; Kripke et al., 1983a,b), but the initial trials of one single hour of bright light could not reflect the full benefit which we now know can be obtained with a week or a month of light treatment. Usage of light treatment is growing in Europe (Kasper et al., 1994), and there is increasing documentation that bright light treatment of nonseasonal depression is useful.

To reassess the clinical applicability of bright light treatment for nonseasonal depression, the more extensive clinical trials now available were reviewed. To offer a comparison, the benefits of light treatment for winter depression and the benefits of antidepressant medications were more briefly examined. Comparison between trials can be useful in appraising the magnitude of bright light benefits, but we should not be overly concerned with the relative benefits of monotherapies if combination therapy is superior.

2. Method

The available clinical trials of bright light treatment of nonseasonal major depression were reviewed. Trials were included in which all depressed patients received antidepressant medications or partial sleep deprivation, if in addition, bright light and placebo-light were randomly assigned to balanced groups. Reports lacking a randomized control treatment were omitted, as were reports with so few subjects as to produce an excessive risk of Type II error.

To provide a perspective on light treatment's benefit in nonseasonal depression, light benefits in winter depression were reviewed, with emphasis on the problems of controlling for placebo effects.

It did not seem feasible to review the entire literature on antidepressant drug trials or any sort of representative sample to provide a reference, so two historically distinguished trials of older antidepressants were examined together with several modern trials of contemporary SSRI drugs, in order to illustrate the range of psychopharmacologic results which have been considered successful. Only trials of antidepressant drugs which reported baseline and final scores on the Hamilton Depression Rating Scale (HDRS) were considered to allow comparability with the net benefits of light treatment.

For each clinical trial, the baseline depression rating (e.g., the HDRS score) was considered as the 100% index, and the depression ratings at the end of the trial were computed for active treatment and for control treatment as a percentage of this baseline. Then, the *net benefit* of active treatment was computed as the percentage reduction of depression ratings with active treatment minus the percentage reduction of depression with the control treatment.

3. Results

3.1. Bright light efficacy for nonseasonal depression

Our first studies of bright light tested only one single hour of bright light to treat hospitalized patients with nonseasonal depressions (Kripke, 1981; Kripke et al., 1983a). The light treatment was given from 2 hours to 1 hour *before* the patient's planned time of awakening, so that these patients experienced 1 or 2 hours of sleep deprivation at the end of the night. Most patients were drug free, but some were taking antidepressants during light treatment. As compared to a control hour of dim red light placebo, which presumably produced about the same sleep deprivation, the bright light reduced mood ratings

about 12%. This benefit was statistically significant. As will be seen, a 12% net gain as compared to placebo is similar to benefits achieved by antidepressant medications after weeks of treatment, so it was remarkable that such substantial benefit could be obtained with one single hour of treatment.

In an extension of our initial studies, 25 drug-free patients were treated with bright light several hours each day for 1 week, compared to 26 patients treated with a dim red light placebo (Kripke et al., 1992). Depression ratings were 18% lower after bright light than after placebo, a benefit which was statistically significant. It is important to note that in this study, measured patient expectations for the dim red light placebo were equivalent to those for bright light. These data suggested that 1 week treatment produced more benefit than had been gained with only one hour of bright light. More recently, another 1 week study of unmedicated inpatients observed a somewhat larger net advantage of 24.2%, which was likewise statistically significant (Yamada et al., 1995). This study observed no difference in benefit between morning and evening light treatment. Even a study reporting no statistically significant benefit achieved a 12.2% net advantage in HDRS ratings of the bright-light treated group (Mackert et al., 1991), so the failure to achieve statistical significance could have been a Type II error due to insufficient numbers of subjects. These studies of drug-free depressives were consistent in demonstrating advantages of bright light treatment compared to placebo.

Two European studies were important because they examined the effects of bright light (as compared to a dim-light placebo) in patients who were also receiving antidepressant medications. In both of these studies, the net relative advantage of bright light over dim light was 27% (Prasko et al., 1988; Schuchardt and Kasper, 1992; Kasper et al., 1994). Since the medication-only groups also did well in these combination studies, the additional improvement gained by the light-treated patients was especially impressive. The study of Prasko et al. obtained more benefit with morning than with afternoon or evening treatment, but because the morning treatments were given rather early, some augmentation with early-morning sleep deprivation may have been confounding (Prasko et al., 1988). A third European study likewise demonstrated substantial and significant benefits of bright light compared with placebo among patients simultaneously receiving antidepressants (Reide and Gohlert, 1994), but the net percentage benefit could not be computed because the baseline depression scores were not reported. It is uncertain how well these studies balanced patient expectations between active and placebo treatments. As previously noted (Kasper et al., 1994), the European studies have suggested that effects of antidepressant drugs and bright light in combination might be somewhat synergistic, that is, even somewhat better than additive.

In an additional study, bright light was combined with antidepressant medication and compared both with medication alone and with medication plus sleep deprivation, but unlucky randomization had failed to produce balance between treatment groups at baseline. The light-treated group had the lowest depression ratings but less net benefit after the first week of combined treatment (not significant). Later, after light treatment had been reduced to 3 times per week or less, the medication-only group made more progress (Holsboer-Trachsler et al., 1994). These results are uninterpretable in terms of comparative treatment efficacy, since the group assigned to bright light had significantly poorer prognostic factors. Accordingly, the net benefit could not be reasonably estimated.

A final recent study combined bright light both with medication and with late-night sleep deprivation (Neumeister et al., 1996). With this triple combination of treatments, patients were dramatically improved within 1 day, and the net benefit of bright light after 1 week of treatment was 35.4% as compared to placebo light. The implications of this small study are extremely exciting and consistent with hints in previous studies that late-night sleep deprivation and anti-depressant drugs augment bright light responses (Kripke, 1981; Kripke et al., 1983a; Prasko et al., 1988), but replication studies with this triple-combination treatment are needed to confirm that antidepressant benefits obtained in a single day of combination treatment can be maintained.

In summary, there is now a preponderance of relatively consistent evidence that bright light treatment produces statistically significant net reductions in mood symptoms in the range of 12–35%. In several studies, significant benefits were observed

within 1 week or even less. Moreover, there seemed to be a trend toward greater additive benefit with light when patients were simultaneously receiving both standard antidepressant drugs and late-night sleep deprivation (Kasper et al., 1994).

3.2. Timing and dosage of light treatment for depression

Controlled trials reporting successful treatment of nonseasonal major depression have generally used from 2–3 hours of 2000–3000 lux light. Insufficient informative data on different dose-responses related to varying intensities or durations of exposures are available. Some uncontrolled trials have suggested that more hours per day of bright light or intensities as high as 10 000 lux might have increased efficacy; however, some caution in using the highest intensities may be indicated when patients are simultaneously receiving lithium because of concern with possible retinal damage (Wirz-Justice et al., 1997; Lam et al., 1997). Bright illumination is usually provided by fluorescent fixtures with excellent reflectors and diffusers filtering out most UV light. There is no evidence that ''full spectrum'' light is better than ordinary white fluorescent light. If a ''full spectrum'' fixture radiates substantial ultraviolet light, it would create an increased risk of both skin cancer and cataracts (Taylor et al., 1988).

There is no clear evidence that nonseasonal depression responds better to morning or to evening light treatment, although studies combining morning light treatment and late-night sleep deprivation tend to show superior results. Midday treatment might be preferable for rapid-cycling bipolars (Leibenluft et al., 1995). Nevertheless, it is likely that patients who have trouble falling asleep at night and difficulty getting up in the morning will be most comfortable with light treatment in the morning. The more a patient tends to get up late, the sooner after wake-up time the patient should receive light treatment. In contrast, light treatment in the evening will be better tolerated by patients who tend to fall asleep early in the evening, perhaps while still watching television, and who suffer from early awakening. If a patient reports no symptoms related to sleep timing, the timing of bright light treatment may not be crucial.

There is little evidence that looking directly at the light source produces better results than keeping the light source in the peripheral vision, and so patients have usually been instructed to simply keep a light treatment fixture within the visual field. It is possible to eat, read, or watch television with a light source slightly to the side of the center of focus. Although special hats and visors have been developed to administer bright light treatment, far more convincing success has been reported with box-like fixtures.

Many patients will experience considerable benefit from bright light treatment within one week, or even on the first day, however, increasing benefit may occur as treatment is continued for several weeks (Kasper et al., 1994). Extended treatment beyond 4 weeks has not been studied systematically, but clinical experience indicates that many depressed patients benefit from incorporating bright light into their long-term living patterns.

The major adverse effects of light treatment reported have been the triggering of mania and the energizing of suicidal drive. If a depressed patient has a prior history of mania, the risk of switch into mania might be minimized if a mood stabilizer is given, and if the light treatment is used in the afternoon or evening (Kripke, 1991). Although two cases of suicidal gestures have been reported in SAD patients soon after starting bright light treatment (Praschak-Rieder et al., 1997), and the author is aware of one SAD patient who committed suicide soon after commencing use of a light visor, it is not entirely certain if these adverse events were triggered by light or were spontaneous. Nevertheless, as with other powerful treatments, careful supervision is advised early in therapy.

3.3. Is bright light specific for SAD?

The earliest controlled report of bright light treatment of SAD described remarkable 52% net benefits within 1 week, however, the bright-light-treated patients were given high expectations which were not matched in the placebo-treated group (Rosenthal et al., 1984). A review adding subsequent studies showed diminishing net benefits compared to the initial report (Terman et al., 1989), even though several of the additional studies reviewed may also have failed to adequately equalize placebo expectations or to even balance placebo assignments. Since

clinical trials of SAD have often induced positive expectations with newspaper recruitment, since the volunteers cannot be literally blind to treatment, and since SAD (by definition) tends to remit spontaneously, the problems of biased expectations and placebo responses have continued to be problematic (Eastman, 1990). Another problem has been the popularity of cross-over trials, in which highly significant order-interaction effects may cloud interpretation (Terman and Terman, 1996).

Recently, two clinical trials of SAD patients devoted extremely careful attention to controlling placebo effects in assessing light-treatment benefits. One of these trials showed only a 6.4% net benefit of bright light after 5 weeks of treatment (Eastman et al., 1993, 1996). After 10–14 days, the second trial showed a 35% net benefit of morning light treatment and a 31% net benefit with evening light treatment compared to a placebo dosage of negative ions (Terman and Terman, 1996). Thus, the net benefit for 2–5 weeks of bright light treatment of SAD appears to be in the range of 6% to 35%, when expectations and randomization are carefully controlled.

As shown in Fig. 1, the range between excellent and less dramatic benefits has been similar in studies of nonseasonal depressed patients and SAD patients. Moreover, it appears that responses might be as rapid in nonseasonal patients as in SAD patients. It would appear that factors other than seasonality have determined the varying responsiveness of patient groups in different studies. The responsiveness of winter depressives could be slightly greater than nonseasonal depressives, or perhaps it is roughly

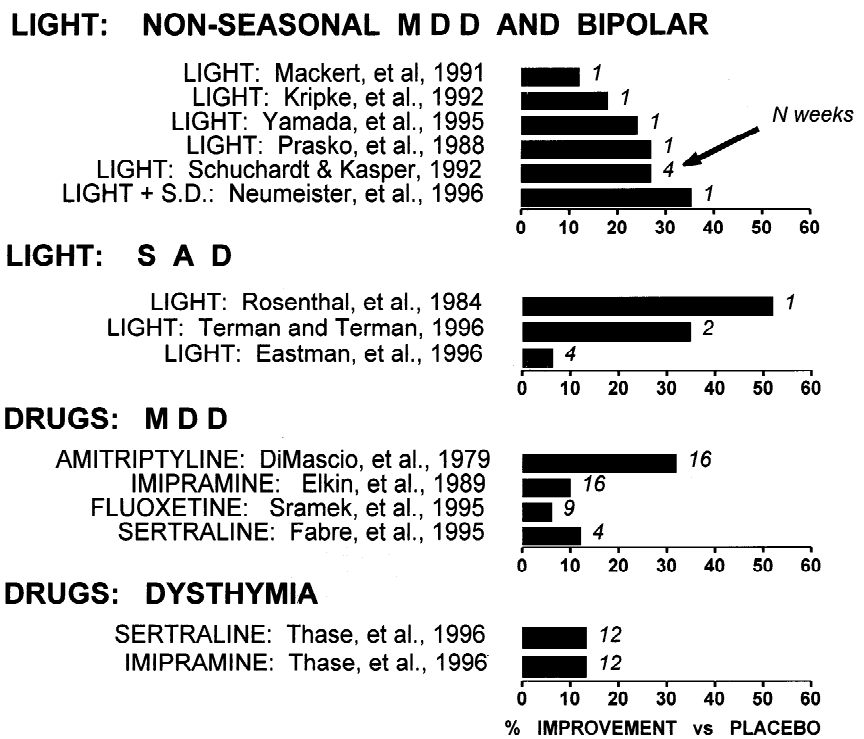

Fig. 1. Net benefits of treatment are compared for studies described in the text. Each bar represents the percentage net reduction in depression ratings from baseline (active treatment percent benefit minus placebo percent benefit). The numbers to the right of each bar represent the number of weeks of treatment. The top six reports described bright light treatments of nonseasonal major depressive disorders. Of these, the first three were studies in unmedicated patients, and the next three were studies of patients who were also receiving antidepressant drugs. The next three reports described bright light treatment of Seasonal Affective Disorders (SAD). The following four studies reported antidepressant drug treatments of nonseasonal major depressions. The bottom study (two bars) reported antidepressant drug treatment of nonseasonal dysthymia.

equal, but the responses in nonseasonal and seasonal depression are certainly in the same range of magnitude.

Most clinical trials of light for winter depression used criteria for SAD offered by Rosenthal et al. (1984), but these criteria have not been accepted by the DSM-IIIR and DSM-IV committees. Follow-up of the prototypal SAD patients by Rosenthal's research group showed that the majority of patients first defined as SAD eventually displayed summer symptoms, if the illness continued to recur (Schwartz et al., 1996). To refer to such a clinical course as ''complicated SAD'' is a euphemism which acknowledges that over follow-up, such patients may be perceived as nonseasonal according to accepted criteria. Many of the prototypal SAD patients eventually required both bright light treatment and antidepressant medications outside the winter months (Schwartz et al., 1996). Because of controversial criteria and complex clinical course, it may often be impossible to define whether a depressed patient does or does not have SAD. Even when a seasonal pattern can be confidently distinguished, there is no assurance that light treatment will work better than in nonseasonal patients, nor does seasonality exclude the usefulness of antidepressant medication in addition to bright light.

3.4. The perspective of antidepressant medications

Hundreds or perhaps thousands of double-blind controlled trials of antidepressant medications have been reported, with a great preponderance of evidence that medicated patients improve somewhat faster than comparison patients given placebo. Nevertheless, many physicians may have the impression that the benefits of antidepressant drugs are greater than such trials actually demonstrate. Because antidepressant medications may require 6–16 weeks to achieve full benefit, patients given placebo for the same interval often display spontaneous remission. The alleviation of symptoms attained during antidepressant drug treatment in many studies may be due more to spontaneous remission than to medication benefit. The modest net benefits of antidepressant drugs are only understood when the percentage remission of symptoms achieved with placebo is subtracted from the remission accompanying medication.

The number and diversity of antidepressant drug trials makes a comprehensive summary impractical. Also, many reports of medication do not permit computation of net benefit, because mood ratings (such as the HDRS) were not explicitly reported both at baseline and at the end of treatment. To illustrate the range of antidepressant drug benefits, the brief analysis below will only review a few particularly distinguished older reports and some newer reports which used the most contemporary compounds and research designs.

In the National Institute of Mental Health's Treatment of Depression Collaborative Research Program trial, although statistically significant, the net benefit of imipramine over placebo was only 10% after 16 weeks, partly because there was over 50% remission in the placebo group (Elkin et al., 1989). Most of the improvement observed was attributable to spontaneous (or placebo) remission during the lengthy research observations, not to the benefits of medication. The net benefits of cognitive and interpersonal therapies were less than 10%. DiMascio et al. (1979) obtained better results: a 32% net benefit with amitriptyline after 16 weeks and a similar net benefit with psychotherapy, but in a large recent study of sertraline, the net benefit of all doses was only 12.2% (Fabre et al., 1995). Patients with major depression treated with fluoxetine showed a net benefit of only 6.2% after 9 weeks in one large study, although this small benefit was found to be statistically significant with 72 patients in each group (Sramek et al., 1995). Treating dysthymia for 12 weeks, both sertraline and imipramine produced 13.4% net benefits as compared to placebo (Thase et al., 1996). The net benefits from these medication studies are also illustrated in Fig. 1.

Fig. 1 shows that the net benefits of antidepressant drugs are of a similar order of magnitude as the net benefits of light treatment for both nonseasonal and seasonal depressives. Specifically, the net benefits of antidepressant medications for nonseasonal depression *are not consistently greater* than the net benefits of bright light. Moreover, the benefits of bright light treatment have often been observed more rapidly than maximal antidepressant medication benefits. Fig. 2 illustrates the rapidity of response for the

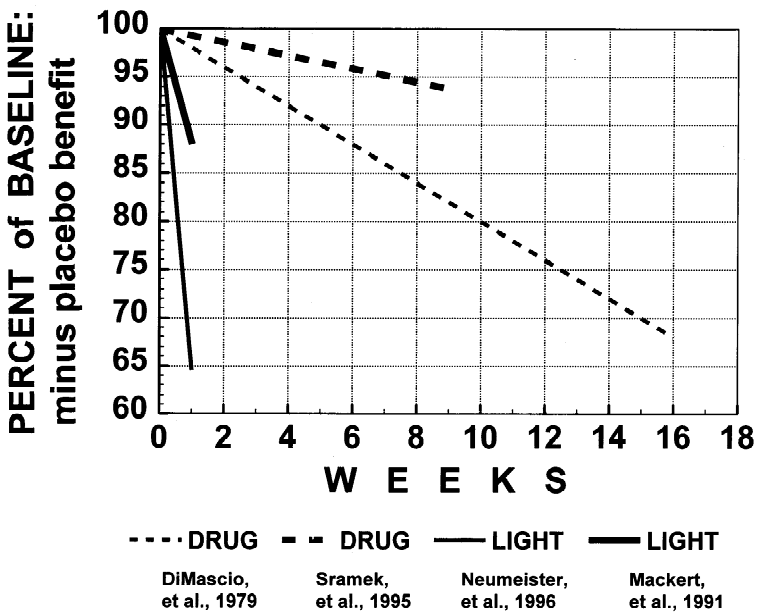

Fig. 2. Of the studies reviewed in the text in treatment of nonseasonal depression, the largest and smallest antidepressant drug effects (dotted lines) are compared with the largest and smallest bright light effects (solid lines). Each line represents the *net* decrease in mood ratings over time, starting with the baseline plotted at 100%. Net benefit was computed by subtracting the percentage reduction of HDRS from baseline for placebo-treated patients from the percentage reduction achieved with the active treatment. The duration of each treatment is plotted on the abscissa.

best and weakest bright light benefits reviewed in nonseasonal depression, contrasted with the best and weakest medication results reviewed, in order to illustrate the relative speed of the responses. Even the worst reported bright light results demonstrated a more rapid speed of response than the best medication results reviewed, as indicated by the steeper downward slope of depression ratings. Rapidity of responses to light might be similar in seasonal and nonseasonal depressives.

Any mistaken impression that bright light benefits are not comparable to medication benefits may have arisen from the brevity of most light studies, which have allowed less time for spontaneous or ''placebo'' remission to occur. During extended intervals of observation, more spontaneous remission and placebo response occurs. If many drug studies have reported a higher percentage of full remissions of nonseasonal depression than bright light studies, it is because the medication studies required more time, not because the net benefits of medication were greater. Similarly, if more complete remissions have been observed in light treatment trials in SAD, it might be because the definition of SAD selects for patients with recent onset and a tendency toward episode brevity.

4. Discussion: contrast or combination of treatments?

The studies compiled in Fig. 1 suggest that bright light benefits may compare favorably with medication net benefits and are probably more rapid, but it might be possible to select other studies in which stronger or more rapid antidepressant drug benefits were observed. Fig. 1 disproves the notion that antidepressant drugs have consistently greater net benefits than bright light, but no conclusive comparison of net benefits of the different treatments should be attempted by comparing unrelated clinical trials. Only direct randomizing comparisons between

antidepressant drugs and bright light could conclusively contrast the effectiveness of these different treatment modalities. A limitation of our current knowledge is the absence of such direct comparisons, together with the lack of long-term controlled trials of bright light. Fortunately, such randomizing comparisons may be unnecessary, since choosing between monotherapies seems neither necessary nor desirable.

In the studies reviewed, bright-light net benefits for nonseasonal depression appeared especially impressive when light effects were added to medication effects. Since light and antidepressant drugs evidently work best in combination, there would generally be no need to choose between antidepressant drugs and light as clinical alternatives. Depressed patients can be offered both the speed of bright light responses and the more extensively verified long-term efficacy of antidepressant medications. Late-night sleep deprivation appears adjunctive to bright light and antidepressant medications, producing an extraordinarily rapid combined response. Clinicians might be wiser to select combined treatment than to try to chose between bright light and antidepressant drugs, even if the comparative data were more extensive.

The combination of light treatment and psychotherapy has not yet been tested in controlled trials, but clinical experience suggests that this combination may also be useful. There seems to be every indication that bright light should be combined with standard therapy except where a depressed patient might be unwilling or unable to utilize the standard treatments.

Cost is not a valid argument against the use of bright light. Outpatient light treatment costs so much less than several months of modern medications or psychotherapy, and light treatment responses are so rapid, that combined treatment is likely to reduce direct treatment costs, even before the cost-savings of abbreviating the patient's disability and morbidity are considered. Introduction of light treatment into managed care should result in cost savings.

In conclusion, sufficient evidence is now available to offer bright light treatment routinely to patients suffering from major depressions, as an adjunct to standard therapies with antidepressant medications and psychotherapy.

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