Author’s response to reviews

Title: Bright Green Light Treatment of Depression for Older Adults

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Author’s response to reviews: see over
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BMC Psychiatry

Dear Friends:

Thank you for the helpful reviews of our manuscripts “Bright Light Treatment of Depression for Older Adults ISRCTN55452501” and “Bright Green Light Treatment of Depression for Older Adults ISRCTN69400161.”

We are pleased to submit revised manuscripts with the benefit of the reviewers’ comments. Detailed responses to the reviewers are attached.

If both manuscripts are accepted, please instruct us if you would wish them to be better integrated, e.g., by reducing repetition of the methods.

Sincerely,

Richard T. Loving R.N., D.N.Sc.
Assistant Project Scientist
We are grateful for the very thoughtful review. We have considered all of the comments in the revision. Here are some detailed responses.

“...discussion is surprisingly brief.”

As suggested, we have expanded discussion of the failure of this clinical trial. As happens with many clinical trials, the investigators do not really know why this trial failed. Even many additional trials might not isolate an explanation. Since there are enough other trials to be confident that bright light treatment is generally beneficial for nonseasonal depression (see the Cochrane systematic review), we now discuss the major possibilities that this age group is resistant to light treatment, that this age group showed insufficient compliance in an outpatient setting, that treatment was not long enough, and that the wake therapy may have interfered. There is also the possibility of plain bad luck, since the power of the study to detect small effect sizes was modest, particularly for each time of treatment.

“...SAD...”

None of the subjects had a seasonal trend as defined by DSM-IV implemented through the SCID, which looks for seasonality. We feel that SPAQ screening would lack specificity for a seasonal disorder as compared with the SCID. Baseline week participant light exposure was slightly (but not significantly) lower in the months of October-March as compared to April-September, which is not surprising in San Diego. Although mood improvements from baseline to the end of treatment were significantly greater in October-March than April-September (p<0.05 if one uses one-tailed tests), that was equally true in both bright and dim-light-treated groups. Analyzing only those subjects treated in October-March yielded no significant light treatment effects or interactions with time of treatment, similar to the year-round data.

Thus, we do not have evidence for a winter-responsive subgroup.

We loosely attempted to eliminate those subjects who reported spending well over an hour a day in daylight. Table 9 indicates that the depressed group were actually exposed to more illumination in baseline than the control group. Although illumination exposure averaged somewhat lower in both depressives and controls in this study than in several of our other subject samples measured in a similar way, it appears that we were not particularly successful in eliminating depressed subjects with relatively high illumination exposure from the treated group. Retrospectively, the group with baseline illumination above the mean had as favorable a response to bright light as those with baseline illumination below the mean.

“I strongly advise for including sleep data in the paper.”

Sleep data are included in the revised manuscript.

1. The purpose of the control group was to demonstrate whether the depressed group, as a whole, was phase advanced or delayed in sleep, melatonin excretion, and illumination
exposure. The depressed group were relatively delayed. This helps us understand that we would theoretically anticipate a better response from morning bright light, although because phase advance has been associated with aging, there would have been an argument that evening bright light would be better. It also helps us understand that the depressed group was not lacking in normal illumination at baseline (see above). We would like to include the control results, because we do believe they are useful in interpreting the clinical trial in the depressed group.

2. As suggested, the abstract was reworded.

3. As suggested, references were added for causes of depression in the elderly.

4. Several references were included to randomized trials of bright light in demented subjects.

5. The description of the melatonin assays was abbreviated as suggested.

6. As suggested, the statement about a trend with p>0.10 was revised, but we do think it is worth communicating that the concomitant treatment has little apparent effect.

7. As suggested, the text was corrected to mention that wake therapy outcomes are given in Table 3.

8. As suggested, the SAFTEE data were split to show results with bright and dim light.

9. (See “1.” above.)

10. The case report was removed from the revised manuscript, but the interested reader could find it if the original manuscript appears on the *BMC Psychiatry* web listing.

11. We appreciate the suggestion to expand the discussion.

12. As suggested, the conclusion was rewritten. However, references 17-22 and additional trials such as Fetveit A, Skjerve A, Bjorvatn B: **Bright light treatment improves sleep in institutionalised elderly-an open trial. Int J Ger Psych 2003, 18:**520-6 do indicate that light may be beneficial in elder samples. Because it was possible ours was just an unlucky trial, or that some aspect of the design such as the wake therapy confounded the results, we do think further trials are needed to clarify when bright light therapy is useful for elder patients.

13. We are not sure if the journal will accept our companion article concerning green light. If both manuscripts are accepted, we hope the editors will guide us as to whether they would prefer the two reports to be a somewhat integrated presentation (e.g., with less repetition of methods) or to appear fully independent.

14. The reviewer has made several good suggestions for the tables. As explained above, we think the control data (as in Table 7) are helpful. Some readers will be quite interested in whether the depressed subjects had delayed onset or offset of melatonin (and which was more delayed) as compared to controls with normal mood, because such phase disorders are being
actively explored as causal elements in depression. In addition, the phase data (particularly the trend for delayed offset) help us evaluate several hypotheses concerning whether morning bright light should have worked.

Bright Light Treatment of Depression for Older Adults ISRCTN55452501

Response to July 14, 2005 comments of Dr. Lewy

We are grateful for the appreciation that negative results should be presented.

We have looked at the phase-angle relationships between aMT6s and sleep. Unfortunately, the numbers of subjects treated with bright light for whom reliable hormone timing data is available is too small to make much of the results. As might be predicted, those whose aMT6s was more delayed in reference to sleep had somewhat better responses to morning light treatment, but the correlation and N were too small to approach significance. Likewise, those with a relatively early aMT6s phase had a better response to evening light, but the correlation was not significant.

As suggested, we have added some hints as to how future protocols might be improved, e.g., a longer duration of treatment or elimination of the wake therapy.
Although brevity is the soul of wit, we appreciate the encouragement of the reviewer to offer somewhat more discussion of the negative findings in this trial. The discussion was also rearranged, as suggested.

As the manuscript explains, there are two likely explanations for the failure to demonstrate a benefit with 1200 lux green light. First, since few even-mild adverse effects were reported, we probably selected too dim a level of green light for maximal benefits/risks. Second, there may well have been a Type II error, since we studied a smaller number of subjects than we know to be desirable. The study was under-powered, but we do not have the resources to extend it. In addition, light resistance in this age group, inadequate compliance, too short a treatment interval, or interfering effects of wake therapy were possible factors. The only way to demonstrate an explanation is to perform more green light trials, which we would encourage.

Regarding SAD, no participants met DSM-IV SCID criteria for seasonal trend. The number of subjects receiving bright green light in this study was too small to explore possible differential response by time of year, but in our previous study of similar subjects treated with bright light, analysis showed no evidence of a seasonal difference in responsiveness. It is quite possible that at higher latitudes, even patients who do not meet criteria for SAD have increased responsiveness to bright light in the winter, as suggested by Martiny K. Adjunctive bright light in non-seasonal major depression. Acta Psychiatr Scand 2004;110(Supplemental 425):7-28. Nevertheless, our group has repeatedly shown that younger depressives in San Diego benefit from bright light treatment.

As suggested, we have expanded the discussion of why the wake therapy failed, pointing out both the poor compliance of this age group and the possibility that wake therapy may be counterproductive at this age. Unfortunately, we had not analyzed the poor compliance obtained in the previous study of the same age group until after this design had commenced.

As suggested, sleep data have now been added to the manuscript, with the remarkable finding that no sleep effect was demonstrable with bright green light. Judging from the literature, the intensity and duration of treatment should have been sufficient for this purpose. Illumination data are also presented, which characterize the exposure levels of the participants in the first week of the study. These overall illumination levels were not impacted by treatment assignment. Few readers will be sufficiently familiar with illumination measurement to understand these data, but essentially they indicate that the general illumination of the subjects was not markedly low (indeed, it averaged slightly higher than in the previous study). No control group was available for this study, but by comparison with the previous study of bright white light treatment and other studies from our laboratory, we infer that the selection method had little impact on the general illumination experience of the participants, which was rather similar to that of the San Diego population.

1. As suggested, the Background in the abstract was expanded.
2. As suggested, the statement about adverse reactions was placed in the results section of the abstract.

3. It is hard to know how much of the review of depression in the elderly should appear in this manuscript, since it would tend to repeat what was said in the manuscript about bright white light treatment. Of course, it depends partly on whether the two manuscripts will be published together. Once a publication decision is made, we hope the editors will advise us as to their preference.

4. The Geriatric Depression Scale was spelled out, as suggested, with the first use of GDS.

5. As suggested, the paragraph comparing this with the previous bright white light study was moved to the introduction.

6. As suggested, the SAFTEE data are now presented separating the bright green light and red light placebo groups.

7. As suggested, the discussion has been expanded.

8. The primary outcome measures, which were the GDS and self-rated HDRS17 at the end of treatment, did favor the green light by about two points. Although this contrast was not significant, it may be because the study had too few subjects. It is true that the 2-week and 4-week follow-ups favored the placebo, but we can now report that the final follow-up (not available at the time of the initial submission) also favored the bright green light.

9.-10. The size of the relative benefit with bright green light at 4-weeks was comparable to the relative benefit over placebo of antidepressants after 8 weeks, that is, 2-3 points on the HDRS (Storosum JG, Elferink AJA, van Zwieten BJ et al. Short-term efficacy of tricyclic antidepressants revisited: A meta-analytic study. *European Neuropsychopharmacology* 2001;11:173-80.) By this standard for a clinically-accepted benefit, the benefits of the bright green light were substantial, though not statistically significant.

11. The helpful suggestions for improving the tables have been incorporated.

We appreciate the many helpful comments of the reviewer.

Bright Green Light Treatment of Depression for Older Adults ISRCTN69400161

Response to July 25, 2005 comments of Dr. Lewy

We are grateful for the kind comments.
Unfortunately, since the numbers were small, correlational analyses relating changes in the phase of sleep to mood changes had too little power to seem worthy of mention. There was no significant association.