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The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression

KLAUS MARTINY[1]*, MARIANNE LUNDE[1], MOGENS UNDÉN[2], HENRIK DAM[3] AND PER BECH[1]

[1] *Psychiatric Research Unit, Frederiksborg General Hospital, Hilleroed, Denmark*; [2] *Psychiatric Specialist Practice, Falkoner Allé, Copenhagen, Denmark*; [3] *Psychiatric Department, Rigshospitalet, Blegdamsvej, Copenhagen, Denmark*

ABSTRACT

Background. Recently accumulated evidence has demonstrated that bright-light therapy in combination with antidepressants is effective in patients with non-seasonal major depression. Whether bright light has a sustained effect after discontinuation is, however, poorly investigated.

Method. In this double-blind randomized study we report the results from a 4-week follow-up period in patients with major non-seasonal depression who had been treated for 5 weeks with sertraline combined with bright-light therapy or sertraline combined with dim-light therapy. At the beginning of the follow-up period the light therapy was stopped while sertraline treatment continued for 4 weeks.

Results. Depression scores decreased substantially in both groups, resulting in high response and remission rates in both groups after 9 weeks of treatment. The difference in depression scores at week 5, favouring the bright-light-treated group, disappeared gradually in the 4-week follow-up period, resulting in similar end-point scores.

Conclusions. Bright light did not have a sustained effect after discontinuation. The offset of effect was complete after 4 weeks.

INTRODUCTION

In this paper we report a 4-week follow-up period in a study assessing patients diagnosed with non-seasonal major depression treated for 5 weeks with sertraline and randomized to either bright white or dim red light therapy. The results from the first 5 weeks showed a statistically significant better outcome for the bright-light-treated group from week 1 and onwards (Martiny, 2004).

We wanted to test in the follow-up period whether bright-light treatment had a sustained effect in the weeks after discontinuation. To the best of our knowledge this issue has not been dealt with before in patients with non-seasonal major depression.

* Address for correspondence: Dr Klaus Martiny, Psychiatric Research Unit, Frederiksborg General Hospital, Dyrehavevej 48, DK-3400 Hillerød, Denmark.
(Email: kmar@fa.dk)

METHOD

Ethics and inclusion

This study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization, Good Clinical Practice (ICH-GCP) Guidelines (EMEA, 1997). The local ethics committee and the Danish Central Data Register approved the study. Patients were referred by general practitioners in the greater Copenhagen area from July 2001 to June 2003.

Exclusion criteria were: patients with seasonal affective disorder, psychotic disorder, organic brain disorder, alcohol abuse and drug abuse of any kind, all according to the DSM-IV

(APA, 1994); in addition, mental retardation, pregnancy or insufficient contraception in females of reproductive age, a history of light-induced migraine or epilepsy, retinal blindness or severe cataract, glaucoma, retinal diseases of the eye, ongoing treatment with antipsychotic drugs, marked suicidal ideation [indicated by a score of >2 on the suicidal item of the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$); Bech *et al.* (1986)], severe agitation (as indicated by a score of >2 on this item of the $HAMD_{17}$) and a score of <13 on the $HAMD_{17}$.

Inclusion criteria were: age between 18 and 76 years (both included) and major depression according to the DSM-IV. Patients with a heart condition, diabetes or previous cerebral insults were allowed to enter the study if in a somatically stable phase.

Psychometrics

The primary outcome scale was the $HAMD_{17}$. Secondary outcome measures were (*a*) the Hamilton six-item subscale ($HAMD_6$), which contains the core depression items (depressed mood, self-depreciation and guilt feelings, work and interests, psychomotor retardation, psychic anxiety and general somatic symptoms) (Bech *et al.* 1981; O'Sullivan *et al.* 1997), (*b*) the Melancholia Scale (MES) (Bech, 2002; Licht *et al.* 2005) and (*c*) seven of the eight 'atypical' items from the Structured Interview Guide for the HAMD, Seasonal Affective Disorders Version (SIGH-SAD) scale (Williams *et al.* 1988), not including 'reverse diurnal'. The diagnoses of major depression and co-morbid conditions were made using the Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan *et al.* 1998). Response to treatment was defined as a reduction of 50% or more of the baseline score on the $HAMD_6$, $HAMD_{17}$ and MES depression scales. Remission was defined as a score of 7 or less on the $HAMD_{17}$, of 4 or less on the $HAMD_6$ (Ruhe *et al.* 2005) and of 6 or less on the MES. As a unidimensional scale (Licht *et al.* 2005), the $HAMD_6$ was included for comparison of response and remission in the two treatment groups at weeks 5, 6 and 9.

Study design

At the start of the study, patients were randomized to two different intensities of light therapy and concomitantly treated with a fixed dose of sertraline. Light treatment conditions were blinded for both researcher and patients. The patients were evaluated at the research unit once a week. In the 4-week follow-up period, light treatment was discontinued while treatment with sertraline was continued with the possibility of increased dosage. Patients were evaluated at weeks 5, 6 and 9.

Light therapy

Patients were randomized to either 10 000 lux white light for 1 hour in the morning or 100 lux dim red light for 30 minutes in the morning. Light was administered by the patients at home every day for 5 weeks. In the follow-up period light was discontinued.

Drug treatment

During the first 5 weeks of therapy a fixed dose of 50 mg daily sertraline was used. In the extension period, the dosage of sertraline could be increased to a maximum of 150 mg if no improvement was observed. Throughout the study time-frame, oxazepam or mianserin were allowed for severe sleep problems or severe anxiety, with maximum daily dosages of 45 mg for oxazepam and 30 mg daily for mianserin.

Statistical analysis

Last observation carried forward (LOCF) was applied for the $HAMD_{17}$, $HAMD_6$, SIGH-SAD and MES scores and for the analysis of response and remission. Thus, all 102 patients included at baseline were considered for analysis. Fisher's exact test was used to test differences in response and remission rates between treatment groups and to test difference in percentage of patient with increased dosage of sertraline. The Mann–Whitney non-parametric analysis was used to test differences in daily sertraline, mianserin and oxazepam dosage (Siegel & Castellan, 1986).

RESULTS

In total, 48 patients were allocated to bright-light treatment and 54 patients to dim-light treatment. After 5 weeks of therapy, 92 patients (90·2%) had completed the study (49 patients in the dim-light group and 43 patients in the bright-light group).

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Table 1. *Sociodemographic data for the 92 patients entering the follow-up period*

	Dim-light group ($n=49$)	Bright-light group ($n=43$)
Age, years, mean (S.D.)	46·3 (15·2)	44·6 (15·6)
Gender (female/male)	32/17	31/12
Height in cm, mean (S.D.)	170 (8·7)	172 (9·0)
Weight in kg, mean (S.D.)	71·3 (14·2)	75·1 (14·7)
Number of previous depressive episodes, mean (S.D.)	4·1 (6·4)	3·8 (6·1)
Percentage of patients with first-episode depression	24·1	29·6
Duration of current depression, months, median (25th and 75th quartiles)	10 (3–21)	8 (3–24)
Smokers (%)	30	44
Causative events of actual or previous major depression (%)	85	79
Increased sertraline dose above 50 mg daily (% of baseline patients)	70·4	68·8

Table 2. *Mean depression scores on the $HAMD_{17}$, $HAMD_6$, MES and the seven atypical items from the SIGH-SAD. Last observation carried forward (LOCF) from start of study (week 0) with standard deviations shown in parentheses*

	$HAMD_{17}$		$HAMD_6$		MES		The seven atypical SIGH-SAD items	
	Dim light ($n=54$)	Bright light ($n=48$)	Dim light ($n=54$)	Bright light ($n=48$)	Dim light ($n=54$)	Bright light ($n=48$)	Dim light ($n=54$)	Bright light ($n=48$)
Week 5	12·2 (5·0)	10·0 (5·7)	7·3 (2·7)	6·1 (3·5)	12·8 (4·8)	11·0 (5·8)	4·2 (1·9)	3·3 (1·9)
Week 6	10·6 (5·1)	10·0 (5·7)	6·4 (2·7)	6·2 (3·6)	11·3 (4·9)	10·5 (5·7)	4·0 (2·1)	3·6 (2·2)
Week 9	8·5 (5·4)	8·1 (6·3)	4·9 (3·1)	4·9 (3·8)	8·5 (5·4)	8·5 (6·0)	3·7 (2·3)	3·7 (4·8)

HAMD, Hamilton Depression Rating Scale; MES, Melancholia Scale; SIGH-SAD, Structured Interview Guide for the HAMD, Seasonal Affective Disorders Version.

During the 4-week follow-up, three patients from the bright-light-treated group each missed one of the three scheduled visits while eight patients from the dim-light-treated group each missed one of the scheduled visits. Thus, during the whole of the follow-up period, 11 of the scheduled 276 visits (92 patients evaluated at three visits) were missed. At the final visit 43 patients (or 87·8%) from the dim-light group and 41 patients (or 95·3%) from the bright-light group were assessed.

The mean daily dosage of sertraline in week 6 was 80·0 mg (S.D. = 24·2) in the dim-light group and 75·6 mg (S.D. = 29·6) in the bright-light group. In weeks 7 to 9 the mean daily dosage of sertraline was 90·4 mg (S.D. = 24·2) in the dim-light group and 90·1 mg (S.D. = 30·9) in the bright-light group. Only a few patients received treatment with mianserin and oxazepam. Thus, the mean daily dosage of mianserin in week 6 was 1·6 mg (S.D. = 6·2, $n=4$) in the dim-light group and 0·9 mg (S.D. = 3·7, $n=3$) in the bright-light group. In weeks 7 to 9 the mean daily dosage of mianserin was 1·7 mg (S.D. = 6·4, $n=4$) in the dim-light group and 1·2 mg (S.D. = 5·0, $n=3$) in the bright-light group. The mean daily dosage of oxazepam in week 6 was 3·1 mg (S.D. = 9·6, $n=7$) in the dim-light group and 3·7 mg (S.D. = 9·2, $n=8$) in the bright-light group. In weeks 7 to 9 the mean daily dose of oxazepam was 3·2 mg (S.D. = 9·7, $n=7$) in the dim-light group and 3·8 mg (S.D. = 9·5, $n=8$) in the bright-light group. No statistically significant differences in daily dosage between the two light therapy groups were found for sertraline, mianserin or oxazepam at any time point.

Table 1 shows sociodemographic data for the two treatment groups entering the follow-up period. No statistically significant differences were found.

Table 2 shows the scale scores on the $HAMD_{17}$, $HAMD_6$, MES and the SIGH-SAD

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Table 3. *Response and remission rates on the $HAMD_6$, $HAMD_{17}$ and MES as percentage of all baseline patients. Response is defined as a 50% or more reduction of baseline scores and remission as a score of $\leqslant 4$ on the $HAMD_6$, a score of $\leqslant 7$ on the $HAMD_{17}$ and a score of $\leqslant 6$ on the MES scale. Last observation carried forward from baseline (LOCF). Numbers of patients are shown in parentheses*

	Response		Remission	
	Dim light ($n=54$)	Bright light ($n=48$)	Dim light ($n=54$)	Bright light ($n=48$)
$HAMD_6$				
Week 5	31·5 (17)	64·6 (31)**	14·8 (8)	31·3 (15)
Week 6	46·3 (25)	54·2 (26)	20·4 (11)	35·4 (17)
Week 9	63·0 (34)	72·9 (35)	51·9 (28)	50·0 (24)
$HAMD_{17}$				
Week 5	40·7 (22)	66·7 (32)*	14·8 (8)	41·7 (20)**
Week 6	63·0 (34)	75·0 (36)	25·9 (14)	35·4 (17)
Week 9	75·9 (41)	79·2 (38)	55·6 (30)	60·4 (29)
MES				
Week 5	29·6 (16)	60·4 (29)**	13·0 (7)	22·9 (11)
Week 6	48·1 (26)	60·4 (29)	18·5 (10)	22·9 (11)
Week 9	70·4 (38)	77·1 (37)	42·6 (23)	43·8 (21)

HAMD, Hamilton Depression Rating Scale; MES, Melancholia Scale.
* $p<0·05$, ** $p<0·01$.

scales. A reduction in depression scores is seen in all scales from week 5 to 9. On all four scales the difference between treatment groups found at week 5 disappeared gradually during the 4 weeks of follow-up, resulting in similar depression scores in both treatment groups at week 9. Thus the effect of bright-light treatment seen after the initial 5 weeks of treatment is lost in the follow-up period.

Table 3 shows response and remission rates at weeks 5, 6 and 9 for the two treatment groups using the $HAMD_6$, $HAMD_{17}$ and MES depression scales. At week 5, statistically significant differences favouring the bright-light-treated group were found for response ($p<0·01$ and $p<0·05$) on all three depression scales. For remission ($p<0·05$), only the $HAMD_{17}$ scale reached statistical significance. These differences disappeared in the follow-up period, resulting in similar response and remission rates at week 9.

DISCUSSION

Treatment effect

On all three depression scales the difference between treatment groups seen at week 5 has disappeared at end-point. The extent of remission is similar on the $HAMD_{17}$ and the $HAMD_6$ but somewhat lower on the MES scale. The MES scale covers retardation in four separate items, assessing verbal retardation, motor retardation, problems with concentration and emotional retardation. The Hamilton scales ($HAMD_{17}$ and $HAMD_6$) have, in comparison, only one item for retardation. Retardation is a symptom that often takes longer to remit, especially in patients with recurrent and long-standing depression as in this sample. Thus the lower remission rates on the MES scale could well be explained by the construct validity of this scale. It should, however, be taken into consideration that the cut-off score for remission on the MES is less well validated than for the $HAMD_{17}$ and the $HAMD_6$. Thus a higher cut-off score would increase the remission rate on the MES scale.

Whether the powerful increase in response and remission rates seen during the 4-week follow-up period would have been obtained if a continued 50 mg daily dosage of sertraline had been used, or whether this increase in response and remission is due to the actual increase in sertraline daily dosage, cannot be settled using this study. A dose–response trial with sertraline has, however, shown that 50 mg daily is the minimal effective dose and that higher doses are not associated with higher response rates (Fabre *et al*. 1995). Our study thus demonstrates the importance of continuing trials beyond the

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5-week acute treatment period, as this allows a much better evaluation of the full antidepressive effect of a drug. Even a 9-week study period could be too short, as further improvement might occur (Bech, 2005).

The lack of sustained effect of bright-light treatment

The fact that the daily sertraline dosages and the concomitant oxazepam and mianserin usage were equal in the two groups of patients in the whole of the follow-up period does imply that the similar depression end-point scores of the two groups must be related to factors other than medication. The discouraging results from the follow-up period are thus that the effect gained by 5 weeks of bright-light treatment is lost a mere 4 weeks after discontinuation of light treatment.

To the best of our knowledge no study has assessed the effect of discontinuation of adjunct light treatment in non-seasonal depression. In studies with light treatment in seasonal depression, the loss of effect after discontinuation of light treatment is, however, a well-known phenomenon, even though some studies have shown a sustained effect even after short light-treatment courses (Wirz-Justice *et al*. 1986; Terman *et al*. 1994; Partonen & Lonnqvist, 1995; Martiny *et al*. 2004). This known loss of effect is the reason why continual light treatment for the whole of the dark season is recommended in seasonal depression (Lam *et al*. 1999). The majority of patients in our study had long-standing current episodes with a median duration of 8 and 10 months in the two groups, and suffered from recurrent depression, with only 24·1% and 29·6% of patients, respectively, in the two groups having first-episode depression (Table 1). Thus, a high relapse occurrence after discontinuation of light might be expected. Whether adjunct light treatment in patients less severely affected by depression would have a more sustained effect can only be decided by future studies in different populations.

Thus the catching-up of depression scores in the dim-light-treated group is best explained by the assumption that, in this study, the 5 weeks of light treatment in non-seasonal major depression worked as having an accelerating modality rather than having an augmenting effect. The observation that the advantage of bright-light *versus* dim light was most pronounced in the first week of the initial treatment period (Martiny, 2004) substantiates this. However, no definite proof of this assumption is possible. This might only be answered in a study in which a third group continued light treatment for the whole of the study period, in order to see whether the superior effect of bright-light treatment seen in the first 5 weeks would last or diminish when continued.

The results from this paper showing that the effect of bright light is quickly lost after discontinuation, together with the fact that light in this as well as in other studies has been found to have an early onset of action in both seasonal and non-seasonal depression (Terman *et al*. 1989; Benedetti *et al*. 2003), imply that the antidepressive mode of action of bright light might be distinctly different from the mode of action of antidepressant drugs.

Analysis on the individual items of the Hamilton scale from the first 5 weeks of this study showed that the differences between the two treatments groups were mostly due to the core depressive items (Martiny *et al*. 2005). An analysis of the seven atypical items from the SIGH-SAD, also from the first 5 weeks of treatment, showed that the differences between treatment groups for these items were only statistical significant for the item 'Social Withdrawal', which is similar to the Hamilton item 'Work and Interest' and thus belonging to the core depressive symptoms. The differences between the two treatment groups on the remaining items on the SIGH-SAD were statistically insignificant (data not shown). Thus the effect of bright light was not seen in the atypical symptoms but in the core depressive symptoms. The effect of bright light would thus seem to be connected to a central regulatory mechanism that affects the core depressive symptoms in a manner different from that operating in the pharmacological treatment of depression.

In conclusion, the results obtained from the full 9-week period of this study support evidence of a transient accelerating effect of bright light in non-seasonal depression. The clinical implications of this study are that bright light in non-seasonal depression should be used to achieve an earlier antidepressive response.

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DECLARATION OF INTEREST

None.

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