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Effects of fluoxetine *versus* bright light in the treatment of seasonal affective disorder[1]

S. RUHRMANN,[2] S. KASPER, B. HAWELLEK, B. MARTINEZ, G. HÖFLICH, T. NICKELSEN AND H.-J. MÖLLER

From the Department of Psychiatry, University of Cologne, Department of Psychiatry, University of Bonn, Department of Psychiatry, University of Munich, and Eli Lilly Germany; and Department of Psychiatry, University of Vienna, Austria

ABSTRACT

Background. Disturbances of serotonergic neurotransmission appear to be particularly important for the pathophysiology of winter depression. This study investigated whether fluoxetine has antidepressant effects comparable to bright light in the treatment of seasonal affective disorder (winter type).

Method. A randomized, parallel design was used with rater and patients blind to treatment conditions. One week of placebo (phase I) was followed by 5 weeks of treatment (phase II) with fluoxetine (20 mg per day) and a placebo light condition *versus* bright light (3000 lux, 2 h per day) and a placebo drug. There were 40 patients (20 in each treatment condition) suffering from seasonal affective disorder (SAD) according to DSM-III-R who had a total score on the Hamilton Depression Scale of at least 16.

Results. Forty patients entered phase II and 35 completed it (one drop-out in the fluoxetine group and four in the bright light group). Fourteen (70%) of the patients treated with bright light and 13 (65%) of those treated with fluoxetine were responders (NS). The remission rate in the bright light group tended to be superior (bright light 50%, fluoxetine 25%; $P = 0{\cdot}10$). Light therapy improved HDRS scores significantly faster, while fluoxetine had a faster effect on atypical symptoms. Light treatment in the morning produced a significantly faster onset of improvement, but at the end of treatment the time of light application seemed not to be crucial.

Conclusion. Both treatments produced a good antidepressant effect and were well tolerated. An apparently better response to bright light requires confirmation in a larger sample.

INTRODUCTION

Seasonal affective disorder (SAD)/winter type is a subtype of affective disorders with recurrent major depressive episodes in autumn/winter (Rosenthal *et al*. 1984; APA, 1987). The typical syndrome is characterized by certain symptoms, e.g. hyperphagia, carbohydrate craving, weight gain and hypersomnia (Rosenthal *et al*. 1984). Despite the ongoing discussion about possible placebo effects (Brown, 1990; Eastman, 1990; Steward, 1990; Eastman *et al*. 1992) light therapy has become the first choice treatment for this type of depression (Oren & Rosenthal, 1992). However, there is a considerable portion of non-responders. In addition, prominent symptoms of SAD, e.g. loss of drive and energy sometimes make it difficult to comply sufficiently with the light regimen.

Little is known about the efficacy of pharmacotherapy in SAD. The treatment of SAD with tricyclic antidepressants has never been tested in a controlled, prospective study. Yet, early studies of SAD reported many patients who responded to light therapy who were unsatisfied with their previous pharmacological treatments (Rosenthal

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[2] Address for correspondence: Dr Stephan Ruhrmann, Psychiatrische Klinik und Poliklinik der Universität zu Köln, Joseph-Stelzmann-Str. 9, 50924 Köln, Germany.

et al. 1984; Wirz-Justice *et al*. 1986). Moreover, SAD symptoms like raised appetite, weight gain and fatigue may be increased by tricyclic antidepressants (Paykel *et al*. 1973). Open studies indicate positive effects of the atypical antidepressant bupropion (Dilsaver *et al*. 1992) or of tranylcypromine (Dilsaver *et al*. 1990), while responses to desipramine turned out to be unstable. In a small study, improvement was achieved with a combination of interpersonal psychotherapy and imipramine (Thase, 1989). In a recent investigation, no significant difference between effects of moclobemide and placebo was found (Lingjærde *et al*. 1993). Antidepressive effects of dexfenfluramin (O'Rourke *et al*. 1989), L-tryptophan (McGrath *et al*. 1990) and citalopram (a single case-report, Wirz-Justice *et al*. 1992) as well as anecdotal reports about trazodone and fluoxetine (Jacobsen *et al*. 1989) suggest that drugs influencing the serotonergic neurotransmission may be effective in SAD. Recently, another study of the efficacy of fluoxetine in SAD was reported not comparing it to light therapy but to placebo (Lam *et al*. 1995); the results of this will be discussed in more detail later.

Studies on the serotonergic neurotransmission indicate that serotonin can be regarded as a central mediator in the pathophysiology of SAD (Jacobsen *et al*. 1989; Skwerer *et al*. 1989). In particular, the eating and sleeping behaviour of SAD patients may be affected by serotonin (Wurtman & Wurtman, 1979; Rosenthal *et al*. 1989*a*; Leonard, 1992). The tryptophan depletion test evoked a marked relapse in light-treated SAD patients (Lam *et al*. 1996; Neumeister *et al*. 1997), an effect known to occur after treatment with a selective serotonin reuptake inhibitor (SSRI), but not after a catecholamine reuptake inhibitor (Heninger *et al*. 1996).

The close association between SAD symptoms and serotonergic neurotransmission made it reasonable to study the clinical use of a SSRI. Fluoxetine was shown to be an effective antidepressant in several previous studies of the treatment of non-seasonal major depression (Stark & Hardison, 1985; Montgomery, 1989; Kasper *et al*. 1992; Ruhrmann, 1995). In addition, fluoxetine has been reported to be effective in the treatment of atypical symptoms (Reimherr *et al*. 1984) attributed to SAD. Therefore, the aim of our study was to investigate fluoxetine as a treatment alternative to light therapy in SAD.

METHOD

Subjects

Patients were recruited from our out-patient clinic for SAD: attention having been drawn to our clinic by short advertisements in newspapers and interviews and reports in journals and broadcasting. In advertisements, only anergia, lower performance at work, depressive mood and social withdrawal during the autumn/winter period were mentioned as symptoms. At first contact, standardized information was given why light and fluoxetine are assumed to be possible treatment alternatives. Inclusion criteria were a major depression with a seasonal pattern (recurrent episodes during autumn/winter) according to DSM-III-R (APA, 1987), a total score of at least 16 on the 21-items Hamilton Depression Rating Scale (HDRS) at entry and after the placebo phase (first week), and age between 18 and 65 years. Because of the typical SAD symptoms' profile, the three sleep items and the two items regarding appetite and weight loss usually score low in SAD. Thus, with a HDRS score $\geqslant 16$ patients were moderately to severely depressed (Terman *et al*. 1989). Item 17 was omitted, because an attribution of symptoms to external factors (like season) has to be assessed as 'loss of insight' by definition. Most important exclusion criteria were serious suicidal risk, concurrent clinically significant medical illness not stabilized, abnormalities in haematology or liver function test, eye diseases, hypertension treated with reserpine, clonidine, alpha-methyldopa or guanethidine as well as concomitant organic brain disease, history of seizures, psychoses or drug/alcohol abuse within the past 6 months; and use of MAOI, anticonvulsants and neuroleptics within 2 weeks or use of depot neuroleptics within 4 weeks prior to the beginning of the study.

Diagnosis was given using the Structured Clinical Interview for DSM-III-R (SCID, German Version) (Wittchen *et al*. 1990) and ascertained by the Seasonal Pattern Assessment Questionnaire (SPAQ, German version) (Rosenthal & Heffernan, 1986; Kasper 1991) and the Seasonal Screening Questionnaire (SSQ,

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Table 1. *Demographical and clinical characteristics*

	Total group	Bright light group	Fluoxetine group
Number	42	20	20
Sex (F, M)	33, 9	14, 6	17, 3
Age (years)*	41·1 ± 10·6	39·4 ± 11·0	41·9 ± 10·3
Age of onset (years)*	29·4 ± 10·1	28·5 ± 9·2	30·6 ± 10·7
Number of major depression episodes*	10·2 ± 5·3	10·7 ± 3·8	9·6 ± 6·5
Duration of episodes (months)*	5·25 ± 1·18	5·22 ± 1·20	5·19 ± 1·18
Unipolar	34	19	14
Bipolar II	8	1	6
Bipolar I	0	0	0
GAF†*	56·1 ± 6·6	55·0 ± 5·5	57·8 ± 7·3
SPAQ‡ score*	16·5 ± 3·7	16·7 ± 3·2	16·1 ± 4·2
Newcastle score*	6·5 ± 1·2	6·4 ± 1·3	6·7 ± 1·2

* Mean ± S.D.
† Global Assessment of Functioning Scale (DSM-III-R).
‡ Seasonal Pattern Assessment Questionnaire.

German version) (Rosenthal *et al*. personal communication; Kasper, personal communication). For demographic variables see Table 1. The earliest entry into the study on 22 October, the latest on 5 February.

At the beginning of the placebo week, 26 (65%) patients had been free of psychotropic medication for more than 6 months. The other 14 patients were equally distributed among both treatment groups. Washout periods were (mean days ± S.D.): fluoxetine 18·1 ± 28·3 days (median 7 days, range: 0–80 days), bright light 12·0 ± 14·8 days (median 7 days, range: 0–44 days), difference NS.

Procedure

The study fulfilled the requirements of good clinical practice. It had the approval of our ethic's committee and was regularly monitored. All patients gave their written informed consent. Fluoxetine (FLU) was used in a fixed dose of 20 mg per day, taken in the morning (Bressa *et al*. 1989; Wernicke *et al*. 1989). The method of light treatment was analogue to the procedure described in the literature (Kasper *et al*. 1989*a*; Rosenthal *et al*. 1989*b*; Avery *et al*. 1991). A fluorescent white light was used. The light boxes (Theralux™ ATL-8, SML, Aachen, FRG) measured 0·75 × 0·46 × 0·20 m; 3000 lux (bright light condition, BL) were emitted through a special diffusing screen (produced by Röhm-Plastik) at a distance of 0·55 m. To ensure tolerability, the frequency of flickering was transformed up to 20 MHz. As placebo condition, dim light (100 lux, DL) was used (Rosenthal *et al*. 1989*b*; Terman *et al*. 1989): it was produced by decreasing the transparency of the diffusing screen and increasing the distance to the screen to 1·5 m. Treatment was carried out at home by glancing at the light box approximately once a minute for a few seconds. Initially, patients could choose between three light application schedules: (1) 2 h in the morning; (2) 2 h in the evening; or (3) 1 h in the morning plus 1 h in the evening. A maximum 1 h advance on usual waking time and a minimum 1 h interval prior to sleeping time was permitted. Thus, we tried to avoid possible confounding effects by sleep deprivation or disturbances. Therefore, patients who started to work early in the morning were unable to choose the first option.

To enhance and document compliance, we asked the patients to complete the Stanford Sleepiness Scale (Hoddes *et al*. 1973). They had to note the actual time, their activities and their subjective alertness level every 15 min while receiving light treatment.

At the beginning and the end of the study, laboratory controls including blood cell count, biochemical standard parameters from serum and urine, screening for antidepressants and blood levels of fluoxetine and norfluoxetine as well as a full physical examination including the eyes and an ECG were performed. Body weight, heart rate and blood pressure were recorded weekly.

Design and response criteria

A controlled balanced parallel design was used. Treatment conditions were unknown to the patients. All objective observer ratings of the study were done by one rater (B.H) who was blind with respect to study design and treatment conditions.

The first part (1 week, phase I, visit −1 to visit 0) was designated to control for placebo response and, in addition, as a drug wash-out phase. The patients received a placebo capsule and dim light (2 h per day). Placebo non-responders (HDRS-score ⩾ 16) were randomly assigned to the two treatment groups. Drop-outs during phase I were replaced. In the second part (5 weeks, phase II, visit 0 to visit 5), group 1 was treated with a combination of fluoxetine and dim light

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(2 h per day). Group 2 received a combination of bright light (2 h per day) and a placebo capsule.

Only chloral hydrate or oxazepame were permitted as concomitant psychotropic medications. For those patients who had to change from dim light to bright light in phase II, we had to create a cover story. After the placebo week we told the patients dim light would have been necessary to get their eyes used to the light. Furthermore, before starting the study, we told all patients that it was not the light intensity but the combination of wavelengths that would be decisive for the effect. Thus, the placebo light condition would be achieved by a modulation of wavelength unrecognizable by them. This cover story was possible, because at the time of the study (autumn/winter 1991/92 and 1992/93), light therapy was still a new treatment method in Germany and little to nothing was known about it in public. 'Response' to treatment was defined as a reduction in the combined HDRS- and HDRS-Supplement (HDRS/SUPP) scores from the beginning of phase II to at least 50% at end of treatment. 'Remission' was defined by the criteria as proposed by Terman *et al.* (1990): (*a*) score reduction $\geqslant 50\%$, as described for response; and (*b*) scores $\leqslant 7$ on the HDRS and on the HDRS-Supplement for SAD; or (*c*) $\leqslant 2$ or lower on the HDRS and $\leqslant 10$ on the HDRS-Supplement for SAD.

Ratings

Treatment effects were assessed weekly by the Hamilton Depression Rating Scale (HDRS, 21-items version, item 17 omitted, see above) (Hamilton 1967, the 7-items-Supplement to the HDRS (SUPP) (Rosenthal & Heffernan, 1986) and the Hypomania Scale (Kasper *et al.* 1989*b*). As self-rating scales, the profile of Mood States Scale (POMS, German version) (McNair *et al.* 1981; CIPS 1986) and the Adjective Mood Scale of von Zerssen (Bf-S) (von Zerssen *et al.* 1970) were applied. The SUPP adds symptoms typical for SAD to the HDRS: fatigue, social withdrawal, increased appetite, increased eating, carbohydrate craving, weight gain and hypersomnia (range of scores: 0–23). The Hypomania Scale was applied to assess manic symptoms described in the literature as possible side-effects of both treatments (Rosenthal *et al.* 1989*b*; Ruhrmann, 1995). Pre-treatment expectations about light therapy were evaluated to control for demand characteristics (Orne, 1962). The Expectations Rating Scale (described in Kasper *et al.* 1989*a*) includes a four-items questionnaire and a visual analogue scale. Patients completed the scale before entering phase I, after their first look at the dim light. Patients of the bright light (BL) group repeated the scale before starting with phase II, after their first look at the bright light.

Statistical procedures

WINSPSS 6.01 was used for statistical analyses. For drop-outs, the last observation was carried forward to the end of phase II (intend-to-treat analysis). The term 'baseline' is used synonymous to visit 0 of phase II.

Results were considered significant when $P < 0{\cdot}05$ (two-tailed). Distributions of response/non-response or remission/non-remission were compared by fourfold tables (χ^2 test or Fisher's Exact test). In a second approach, treatment effects were evaluated by analysis of variance (ANOVA) with repeated measurements. In case of a significant ANOVA result, one-tailed *t* tests were performed. Threshold criteria for response or remission enhance comparability of results to other studies and facilitate their transfer to clinical practice. In particular, the remission criterion – combining relative and absolute criteria – has the advantage of a strict and reliable gauge of treatment effects (Terman *et al.* 1989). Because this study has also an exploratory character, using the categorical approach only, differences regarding the course of treatment could be concealed, and consequently, overlooked. To avoid this, changes in scores were also analysed.

The effects of morning and evening light treatment were compared by the Mann–Whitney *U* test. Effect sizes (d, w) were calculated according to Cohen (1988) for within-group changes between first (baseline) and final visit of phase II, and for the significant between-group comparisons. Power calculations were performed with STAT-Power 2.0 (Bavry, 1991).

RESULTS

A total of 42 patients was included in the placebo phase (two patients had to be replaced before starting phase II, one because of spontaneous remission, the other because of doubtful

Table 2. *Psychometric changes during treatment with either fluoxetine or bright light* (*each visit was* 1 *week apart*)

	Fluoxetine ($N = 20$)			Bright light ($N = 20$)		
Visit	HDRS/SUPP†	HDRS	HDRS-Suppl.	HDRS/SUPP†	HDRS	HDRS-Suppl.
−1	37·6±5·2	24·8±4·3	12·8±3·8	39·5±6·6	26·4±4·1	13·2±4·3
0	34·4±6·5**‡	23·2±4·3*	11·3±4·3*	34·6±5·4**	22·7±4·0**	11·9±4·0*
1	29·9±8·6*	20·9±6·5 NS	9·0±3·3*	26·2±9·0***	16·4±6·6***	9·8±4·6*
2	23·3±9·2***	16·8±6·4**	6·5±3·9***	21·9±8·1**	13·3±6·9**	8·7±3·7 NS
3	19·7±8·7*	13·4±5·6**	6·3±4·3 NS	22·1±9·0 NS	14·3±7·0 NS	7·8±3·9 NS
4	16·2±8·8*	10·9±6·1*	5·4±4·0*	18·4±10·6*	12·1±8·5*	6·3±3·7 NS
5	15·6±8·2 NS	10·0±5·7 NS	5·6±4·0 NS	14·0±10·5**	9·3±8·1*	4·7±3·4*

† Combined score of HDRS and HDRS-Supplement.
‡ Paired t tests (one-tailed) (*$P < 0{\cdot}05$; **$P < 0{\cdot}01$; ***$P < 0{\cdot}001$) comparing the mean scores of two successive visits.

compliance). The combined HDRS/SUPP scores (BL, 12·4%; FLU, 8·5%), the separate scores of HDRS (BL, 14·0%; FLU, 6·5%) and SUPP (BL, 9·9%; FLU 11·7%) significantly improved (Table 2). The self-rating scales revealed a significant improvement for the POMS subscale 'vigour' only. No significant group difference was found for any score at visit −1 or visit 0 (baseline of phase II). Forty patients (Table 1) entered phase II, 35 completed it. Demographic variables did not significantly differ (Table 1). Fourteen (70%) of the BL and 13 (65%) of the FLU patients fulfilled the response criterion (χ^2 test, NS). Remission was observed in 10 (50%) BL and in five (25%) FLU patients. This difference was significant at the 10% level ($\chi^2 = 2{\cdot}67$, $P = 0{\cdot}10$). The effect size (ES) was $w = 0{\cdot}26$ ($w = 0{\cdot}1$, small ES; $w = 0{\cdot}3$, medium ES (Cohen, 1988)). The observed power was 0·50. ANOVA with baseline (visit 0) and post-treatment (visit 5) scores revealed a significant time effect (time effect, $F(1, 38) = 125{\cdot}0$, $P < 0{\cdot}001$; group effect, $F(1, 38) = 0{\cdot}2$, NS; group × time interaction, $F(1, 38) = 0{\cdot}3$, NS). Scores decreased by 59·4±27·6% (mean ±S.D.) in the BL group and by 51·9±29·7% in the FLU group. The ES was $d = 1{\cdot}94$ in the BL and $d = 1{\cdot}61$ in the FLU group. The observed power for the detection of a significant ($P < 0{\cdot}05$) group × time interaction was 0·52. For scores and results of within-group comparisons between successive measurements see Table 2. To facilitate a comparison of our results with other studies, we will subsequently report separately the results for the HDRS and the SUPP.

A final reduction of the HDRS scores by at least 50% was observed in 13 (65%) FLU patients and in 14 (70%) patients of the BL group (χ^2 test, NS). ANOVA including all six visits of phase II revealed a significant time effect and a significant group × time interaction (time, $F(5, 34) = 46{\cdot}9$, $P < 0{\cdot}001$; group, $F(1, 38) = 0{\cdot}2$, NS; group × time, $F(5, 34) = 2{\cdot}7$, $P < 0{\cdot}05$). After visual examination of group mean differences, *post hoc* comparisons were restricted to visit 1 and 2. At visit 1, they revealed a significant difference between both groups (Fig. 1*a*). with a lower mean score of the BL group ($t_{1t} = 2{\cdot}2$, df = 38, $P < 0{\cdot}05$, ES $d = 0{\cdot}67$, see Table 2). A similar trend was observed at visit 2 ($t_{1t} = 1{\cdot}7$, df = 38, $P = 0{\cdot}054$). A final reduction of the SUPP score by at least 50% was achieved in 11 (55%) cases in the FLU group and in 13 (65%) cases in the BL group (χ^2 test; NS).

A significant time effect as well as group × time interaction was revealed for all six visits of phase II (ANOVA: time $F(5, 34) = 13{\cdot}7$, $P < 0{\cdot}001$; group effect, $F(1, 38) = 0{\cdot}02$, NS; group × time interaction, $F(5, 34) = 3{\cdot}17$, $P < 0{\cdot}05$). In *post hoc* comparisons restricted to visit 1 and 2 for same reasons as above, the mean score of the FLU group was significantly lower at visit 2 ($t_{1t} = 1{\cdot}79$, df = 38, $P < 0{\cdot}05$) (Fig. 1*b*, Tables 2). ES was $d = 0{\cdot}55$. In further analyses, the SUPP subscores of the appetite and weight related items were significantly different (FLU < BL, $t_{1t} = -2{\cdot}98$, df = 38, $P < 0{\cdot}01$), but not the subscores of the other items.

Hypomania scores did not change significantly throughout the study. Clinically, there was one patient with a short episode of mild hypomania during BL therapy who remitted without change of the treatment schedule. All self-rating scores (POMS, Bf-S) improved significantly; no sig-

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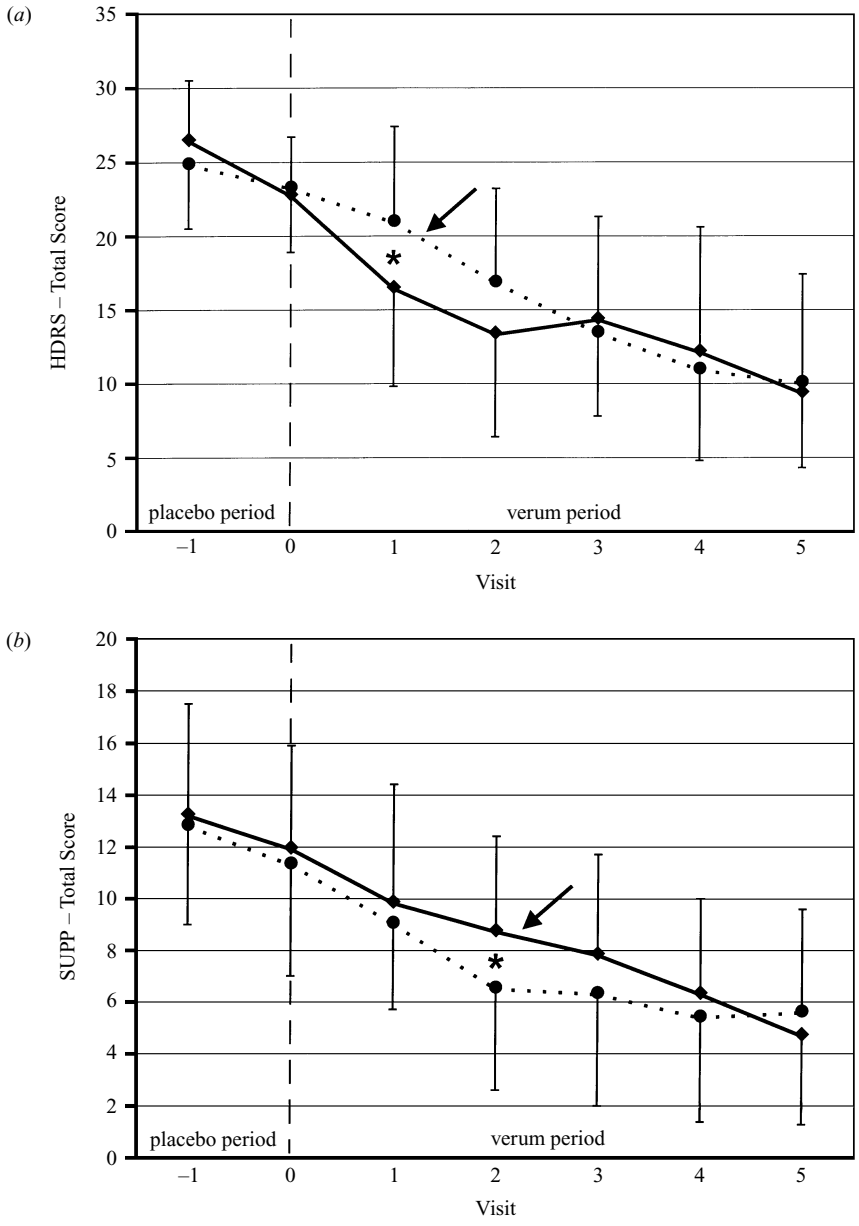

FIG. 1. Course of scores at phase I (placebo drug + dim light) and phase II (fluoxetine + dim light (●···●) *versus* bright light + placebo drug (◆——◆), $N = 20$ for each condition). (*a*) HDRS and (*b*) HDRS-Supplement for SAD. There was a significant difference between the treatment groups at visit 1 and a corresponding trend at visit 2 in (*a*), and a significant difference at visit 2 in (*b*).

nificant difference was observed between treatment conditions. For baseline expectations about light treatment, no difference proved to be statistically significant – neither between treatment groups nor between responders and non-responders. Taking the subscores of the Expectation Scale as covariates (ANCOVA) and the scores of HDRS/SUPP, HDRS and SUPP as dependent variables has had no effect on the significances described so far. Between first and

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second assessment of the Expectation Scale in the BL group, no significant differences were observed.

Time of day

Twenty-four patients received light treatment in the morning (morning subgroup (MG): FLU, $N = 12$; BL, $N = 12$), 13 in the evening (evening subgroup (EG): FLU, $N = 8$; BL, $N = 5$) and three in the morning and evening (morning + evening subgroup (MEG), all BL). The portions of responders per subgroup were not statistically different within the FLU group (responder/subgroup: morning 8/12; evening 5/8) or within the BL group (responder/subgroup: morning 10/12; evening 2/5; morning + evening 2/3). Because of its small size the MEG was excluded from further calculations.

Final scores and relative changes of HDRS/SUPP, HDRS and SUPP scores (score at visit 5/score at baseline) of MG and EG were not significantly different within the FLU or BL group (Mann–Whitney *U* test).

After the first visit, a significant larger relative change of HDRS scores (score at visit 1/score at baseline) emerged in the bright light MG ($37{\cdot}7 \pm 22{\cdot}4\,\%$) than in the bright light EG ($7{\cdot}8 \pm 15{\cdot}9\,\%$; $P < 0{\cdot}05$, Mann–Whitney *U* test).

The portion of patients within the BL group showing a 50% reduction of the HDRS after 1 week was 25% in the MG and 0% in the EG (NS), after 2 weeks it increased to 58·3% in the MG, but remained 0% in the EG ($P < 0{\cdot}05$, Fisher's Exact test: $\phi = 0{\cdot}54$, $w = 0{\cdot}54$, $P < 0{\cdot}05$). The corresponding HDRS/SUPP and SUPP scores differed not significantly.

Starting treatment earlier or later during the autumn/winter period may confound treatment effects. Therefore, the time between 15 October and 16 February was subdivided in four equal time periods. Number of starts per period did not differ significantly. Furthermore, start-up-period and type of treatment or response/non-response had no significant correlations. Also, HDRS, SUPP and HDRS/SUPP scores at baseline and after treatment as well as the relative change of these scores did not significantly differ between the four subgroups.

The two procedures to control for compliance – counting of the returned capsules and the Stanford Sleepiness Scale – indicated one relevant protocol deviation, i.e. a BL patient stopped taking the placebo capsules. Both treatments were well tolerated, there were no serious or withdrawal provoking events. One BL patient who dropped out later needed a co-medication with oxazepam up to 50 mg/day, because of agitation, which was present before the start of the study. Two patients (one BL, one FLU) were treated with chloral hydrate, 500 mg/day, because of sleep disturbances during the first 2 weeks. During phase II, four BL patients (one responder, three non-responders) and one FLU patient (a non-responder) dropped out (NS).

DISCUSSION

This study compared the treatment of seasonal affective disorder with an antidepressant drug to bright light therapy in a parallel design. Furthermore, the effects of light therapy were investigated not only over 1 or 2 weeks, as usual in bright light studies, but over a much longer observation period, as usual in pharmacological trials (Quitkin *et al*. 1984; Pande & Sayler 1993).

Response rates – 65% for fluoxetine and 70% for bright light – are in line with those reported in other studies of light treatment in SAD (Terman *et al*. 1989) or in studies of fluoxetine in non-seasonal depression (Pande & Sayler, 1993). Furthermore, with $d = 1{\cdot}61$ in the fluoxetine group and $d = 1{\cdot}94$ in the bright light group, there was a large effect size (Cohen, 1988) in each group. Thus, in both treatment groups a marked and comparable improvement was achieved.

The difference of remission rates – 25% for fluoxetine and 50% for bright light – was significant on the 10% level, indicating a trend for a superior effect of bright light. The remission rate of the bright light group corresponds with the results of other studies (Terman *et al*. 1989). For fluoxetine, no comparable data are available.

To allow for the comparability of our results to other studies and to detect possible different treatment effects on typical and atypical symptoms, we also analysed HDRS scores and SUPP scores separately. The earlier onset of improvement of HDRS scores in the bright light group is concordant with the literature. Positive effects of bright light are usually observed during the first week, whereas response to fluoxetine

typically begins within 2 to 4 weeks of treatment (Stokes, 1993). The earlier improvement of atypical symptoms (SUPP) in the fluoxetine group was due to the appetite-related items, probably caused by the anorexic properties of fluoxetine (Ruhrmann, 1995).

The lack of a 5% significance for differences between response rates as well as between remission rates may be caused by type II error due to our sample size producing a low power. With our sample size, a difference of eight cases of response or remission would have been the least required to achieve a 5% α level with a power of 0·80. To confirm our results for remission rates (difference of five cases), in a second study, it would be necessary to increase the sample size to $N = 118$ (power 0·80, $P < 0{\cdot}05$). However, response and remission rates are relatively high when compared with other studies of antidepressants and, thus, ceiling effects may well be responsible for reaching only 10% significance. As already mentioned, another important aspect of our study is the long observation period of light treatment. Because improvement continued to proceed until the end of the study (Table 2), treatment periods of 5 weeks seem to be indicated, before a patient is classified as a non-responder. Such treatment periods raise the question of 'spontaneous' remission, especially with the passing season. It seems unlikely that our results have been influenced by the progression of the season, because no significant difference appeared between results when related to the month of treatment. Our results are limited by the fact that we were not able to study a control group that received placebo only. With the placebo lead-in phase, we tried to eliminate possible early placebo responders (Prien & Levine, 1984). This seems reasonable particularly for studies of light treatment, because the standard treatment period in these studies is usually 1 week without any lead-in phase. However, a placebo lead-in phase will not replace a real placebo group, and conclusions remain limited by this fact. The sensation of doing something against the disorder, symbols (e.g. a technical device (light box), a time consuming procedure and a pill taking process), as well as the weekly contact to the clinic may have contributed non-specifically to the improvement. It has been questioned, if dim light is really inert, as demanded for a placebo (Eastman 1990). In our study, the slight improvement during the first week seems to indicate that our dim light condition did not work as a specific treatment at least during this period. Furthermore, the slight placebo response during the first week is in line with Lam *et al.* (1995) who used only placebo capsules in the first week. In antidepressant drug trials, 56% of drug-treated and 30% of placebo-treated patients improved (Klerman & Cole 1965; Quitkin *et al.* 1984). To evaluate the efficacy of a test drug compared with a standard treatment, Quitkin & Rabkin (1981) suggested a 20% to 40% improvement as a guideline for placebo effects. In a meta-analysis of fluoxetine trials (Pande & Sayler 1993), the response rate was 60% in the fluoxetine group (our study: 65%) and 37% in the placebo group ($P < 0{\cdot}001$). A review by Terman *et al.* (1989) revealed a mean response rate of 21% for the dim light control condition compared with a rate of 66% for bright light. The mean remission rate of the dim light controls was 11%. Here again, our results are considerably higher than the placebo rates. Moreover, bright light produced higher rates of improvement than fluoxetine. Such transfers of results should of course be handled with care, but they may provide an important context for the interpretation of single studies. Meanwhile, Lam *et al.* (1995) carried out a second study on the efficacy of fluoxetine in SAD, comparing it with placebo, but not with light therapy. In their repeated measurement analysis, no significant difference between fluoxetine and placebo was ascertained. In contrast, after stratification of the sample in mildly, moderately or markedly depressed subgroups, fluoxetine was significantly superior to placebo in the markedly depressed group. Moreover, when referring to response – as defined in our study – fluoxetine produced a significantly higher response rate (59%) than placebo (34%) with regard to the whole sample. It seems noteworthy that none of our patients would have belonged to the mildly depressed group, but that 50% to 55% of our sample would have been classified as markedly depressed. Furthermore, the mean HDRS scores in our sample were remarkably higher (25·6) than those reported from the other study (18·6). Thus, if a relationship between a true drug response and a more severe depression exists (Quitkin *et al.* 1987; Brown *et al.* 1992) it would

be even more likely that our results are based on specific treatment effects. It is still controversial, if the time of light application is crucial for treatment effects (Wehr *et al*. 1986; Sack *et al*. 1990; Avery *et al*. 1991; Wirz-Justice *et al*. 1993). In a meta-analysis (Terman *et al*. 1989), morning light was superior to evening light for the mildly (HDRS $\leqslant$ 16), but not for the moderately-to-severely (HDRS $>$ 16) depressed cases. Because our patients belonged to the latter, it was possible to offer three light schedules. Our results indicate that bright light in the morning should be the first line recommendation, since it achieved an earlier onset of improvement than the other light schedules – a time-related difference that appears to be unlikely for a placebo. For the final outcome, the time of application seemed not to be crucial. Thus, it can be tried to adapt the light schedule to the needs of the patients. This should avoid a cut-back of efficacy due to poor compliance under naturalistic conditions. However, due to the small size of the subgroups a type II error might be responsible for the observed lack of significant difference.

Compared with 1 or 2 week trials (Terman *et al*. 1989), patients improved slower in our study. Corresponding results were recently reported from the only other published light study of comparable treatment duration (Bauer *et al*. 1994). This general delay may partly be due to the slower improvement in the evening light group as well as to the reduction of non-specific effects of the placebo-lead-in phase. Furthermore, a planned treatment duration of only 1 or of several weeks can raise different interpersonal expectancy effects (Harris & Rosenthal 1985), because it gives the patients an important information about the researchers own expectations. This may also have influenced response rates during the placebo week.

In conclusion, both, bright light and fluoxetine, produced a high and comparable rate of responders. Using the stronger criterion of remission, bright light tends to be the superior treatment. However, as shown above, larger study samples are needed for a final decision. Morning treatment led to an earlier onset of improvement, but the time of day was not crucial for final outcome. In addition to the investigation of a larger sample, in the future, a study allowing for higher dosages of fluoxetine should be carried out, because 20 mg – recommended for non-seasonal depression – may not be the optimal dosage for the treatment of SAD. Furthermore, possible psychopathological or biological response predictors for the different treatment modalities, including phase typing (Lewy *et al*. 1989), should be investigated. The positive effects of fluoxetine as an SSRI supports the hypothesis that serotonin plays a nuclear role in the pathophysiology of SAD. A possible mechanism might be a disturbance of serotonergic signal transduction in the suprachiasmatic nucleus where the 'internal clock' appears to be located. Results from bright light treatment seem to indicate that there is a serotonergic basal tone that is necessary to respond to this treatment (Ruhrmann *et al*. 1994). Perhaps, fluoxetine works by elevating this basal tone over a threshold so that the natural light can be effective again. This would implicate that non-responders to bright light therapy might benefit from the augmentation with fluoxetine.

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