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ORIGINAL PAPER

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Side effects of adjunct light therapy in patients with major depression

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Abstract Adjunct bright-light therapy has been suggested to augment antidepressant drug treatment in patients with non-seasonal major depression. Side effects of the combined therapy have not been investigated thus far. Therefore, somatic complaints and side effects of combined therapy were evaluated in 28 patients with major depression (DSM-III-R) randomly assigned to either trimipramine or trimipramine and serially applied adjunct bright-light therapy. Response rates were comparable in both treatment groups and rates of newly emergent side effects during treatment were generally low. The most prominent unfavourable side effects of adjunct bright-light therapy as compared with trimipramine monotherapy were aggravated sedation, persisting restlessness, emerging sleep disturbance and decreased appetite as well as the worsening of vertigo. Discriminant analysis revealed that the combination of trimipramine with bright light results in a different side effect profile compared with drug monotherapy.

Key words Bright-light therapy · Side effects · Major depression · Adjunct therapy

Introduction

Bright-light therapy (BLT) is considered an effective treatment in patients suffering from seasonal affective disorder (SAD) [26]. The mechanism of action is, however, not yet completely understood. Preliminary data suggest actions on circadian rhythms including phase-shifting and amplitude-modulating properties [4, 11, 16]. Light is assumed to act on melatonin secretion and metabolism via the retinal-hypothalamic-pineal pathway [28]; serotonergic effects of bright light have also been proposed [19, 20]. According to the phase-shift hypothesis, BLT administered in the evening should delay the phase-advance of circadian rhythmicity which was proposed for patients with non-seasonal MDD [10, 16]. Durations of 1–2 h daily with full-spectrum bright light of 2500–5000 lux for 1 week are regarded sufficient for treatment responses [8, 27]. However, accepted guidelines for duration and dosage of BLT in MDD patients are not established thus far.

Besides its therapeutic effects in SAD patients bright light is also a non-pharmacological candidate for adjunct treatment in nonseasonal major depressive disorder (MDD) to augment the efficacy of antidepressant drugs [9, 14, 23] and partial sleep deprivation [17]. However, due to clinical evidence, the efficacy of adjunct BLT in MDD patients is equivocal thus far [24, 29, 31]. A major argument in favour of non-pharmacological adjunct treatments is their assumed safety, an issue which has to be evaluated empirically. Regarding BLT, few systematic reports are presently available [8, 12, 15, 18, 30]. The results indicate BLT to possibly catalyze switches from depression to (hypo-)mania, and to cause several less severe side effects such as headache, eye strain, and irritability, which should not be disregarded.

Compared with other treatments, however, BLT rarely led to treatment discontinuation and was generally assumed to be well tolerated [21]. Nevertheless, the current state of research is incomplete and there are some restrictions of interpretability of the available data: some studies lack a control group, one study used light visors [15] and may therefore be specific to that technique, and the investigated duration of BLT was limited to 1–2 weeks. The relationship between duration of treatment and occurrence rate of side effects is unclear. However, the emergence of side effects of BLT appeared to be independent of light intensity and treatment response [15]. To our knowledge, no previous study has focussed on the side effects of adjunct BLT in patients suffering from non-seasonal MDD.

As pharmacotherapy is the standard treatment in MDD patients, the question should be raised as to whether ad-

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junct BLT changes the side effect profile of an antidepressant drug. Additionally, MDD patients often suffer from a variety of somatic complaints which could either positively or negatively be influenced by treatment side effects. Thus, depressive symptoms, side effects of antidepressant drug therapy and of adjunct BLT might interact in MDD patients. The treatment of severely depressed MDD patients with either trimipramine monotherapy or combined trimipramine and BLT yielded comparable response rates for both treatment modalities [7]. The present evaluation of this study compared side effects of 4 weeks adjunct BLT to a monotherapy with trimipramine. To investigate the safety of adjunct BLT and the side effects of combined treatment the following issues were addressed in an exploratory approach:

1. Emergence rates and change scores of side effects during the course of treatment
2. Differences in side effect profiles between trimipramine monotherapy and combined treatment with BLT

Methods

Subjects and study design

The total study comprised 42 patients with non-seasonal MDD according to DSM-III-R [1] randomly allocated to one of three treatment arms [trimipramine monotherapy (TRI), trimipramine and adjunct sleep deprivation, trimipramine and adjunct bright-light (TRI+BLT)] [7]. Any physical illness was carefully ruled out. For the present evaluation only the groups TRI and TRI+BLT were considered ($n = 14$, each group). Table 1 shows a summary of relevant sociodemographic and psychometric parameters. All patients were severely depressed, ratings of severity of depression [17-item Hamilton Depression Rating Scale (HDRS)] [6] were >18 at week 1 of treatment. All participants gave informed consent prior to the study; the protocol was approved by the local ethics council.

Protocol

Both groups (TRI, TRI+BLT) received standard treatment with trimipramine; at the start of the study (week 1) the previous medication (antidepressants, benzodiazepines, neuroleptics or combinations) was replaced by 100 and 150 mg trimipramine on days 1 and 2, respectively. Pre-treatment was comparable between the treatment groups. From day 3 onwards all patients received 200 mg trimipramine, administered as single dose at 7 p.m. for the rest of the 6-week study period. All patients were treated with trimipramine monotherapy during week 1; group TRI+BLT additionally received BLT during weeks 2–5 of treatment course (Fig. 1).

Light-therapy procedure

Bright light ('full-spectrum', 5000 lux, 2 h, 5:30 to 7:30 p.m.) [2] was administered by means of a light 'wall' containing fluorescent lamps (2.5 m height, 5 m width) in a separate room; the patients were instructed to sit in front of the light wall and glance briefly at the light once or twice per minute while engaged in reading or desk work. The intensity of 5000 lux was achieved by controlling for the distance between the patient's eyes and the light wall (1.5 m). The patients were continually supervised by trained staff. Dosage and frequency of treatments is shown in Fig. 1.

Assessment of side effects

For assessment of side effects a differentiated standard instrument [Fischer's Somatic Symptom/Undesired Effect Checklist (FSUCL)] [3] was used. The FSUCL comprises six different facets of side effect items (central nervous system related, 5 items; gastrointestinal complaints, 6 items; vegetative, 5 items; neurological, 7 items; headache, 1 item; cardiovascular, 2 items) with a total of 26 items. Each item is scored on a 4-point scale, with 0 indicating absence and 3 indicating serious severity. Neurological side effects did not occur and were therefore excluded from analyses. The rating scale was completed weekly at the same time (12.00 h) by a physician blind to treatment modality during a semi-structured interview.

Data analyses

The items of the FSUCL were analysed separately and combined (sum score). As base rates of side effects, FSUCL scores differing from 0 during week 1 (trimipramine therapy in both groups) were

Table 1 Patient characteristics. *TRI* trimipramine monotherapy (200 mg/d); *TRI+BLT* trimipramine and adjunct bright-light therapy; *HDRS* 17-item Hamilton Depression Rating Scale

	TRI	TRI+BLT	Group differences
N	14	14	–
DSM-III-R diagnosis			
296.2	5	4	
296.3	7	8	
296.5	2	2	
Age (years)	50.6 ± 8.5	55.1 ± 10.6	n.s.
Gender (female : male)	5 : 9	9 : 5	n.s.
HDRS			
Week 1	26.0 ± 6.4	22.7 ± 5.2	n.s.
Week 2	19.4 ± 9.2[a]	17.8 ± 6.4[c]	n.s.
Week 5	8.6 ± 8.4[b]	14.5 ± 5.6[d]	$t = 2.2$, $df = 26$, $p = 0.04$
Duration of illness (years)	2.9 ± 3.5	8.0 ± 8.6	$t = 2.1$, $df = 26$, $p = 0.06$
No. of admissions	1.7 ± 0.9	3.6 ± 4.9	n.s.
No. of depressive episodes	2.9 ± 2.1	4.1 ± 5.0	n.s.

Values are mean ± SD
[a–d] Comparisons with week 1 (paired t-test within each group; groups were compared with unpaired t-tests)
[a] $t = 3.9$, $df = 13$, $p = 0.002$
[b] $t = 8.6$, $df = 13$, $p < 0.0005$
[c] $t = 3.8$, $df = 13$, $p = 0.002$
[d] $t = 3.7$, $df = 13$, $p = 0.003$

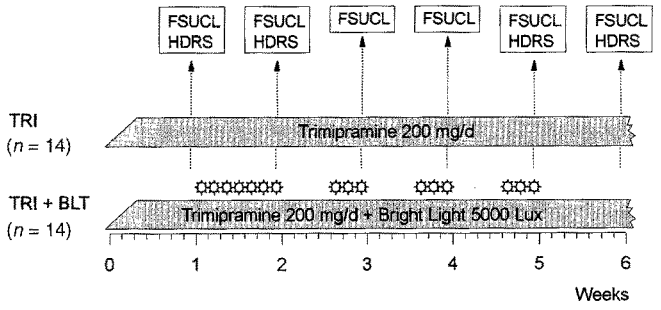

Fig. 1 Study protocol. *TRI* trimipramine; *BLT* bright-light therapy; ☼ bright light (5:30 to 7:30); *FSUCL* Fischer's Somatic Symptom/Undesired Effect Checklist; *HDRS* 17-item Hamilton Depression Rating Scale

recorded. Accordingly, the rates of newly emerging symptoms under ongoing treatment ('emergence rates', i.e. scorings differing from 0 if baseline value was 0) were assessed in week 2 and during the course of week 2 to week 5 (scores differing from 0 for at least 1 week during weeks 2–5). Group differences in symptom frequencies were computed by χ^2 tests. The change in symptoms was expressed as raw score differences between week 2 and 1 (Δ2–1, acute effects), week 5 and 1 (Δ5–1, 4-week effects), and week 6 and 5 (Δ6–5, withdrawal), respectively. The FSUCL variables were analysed for group differences between TRI and TRI+BLT. To detect relationships between antidepressant response and side effects, group differences in FSUCL change scores between responders (improvement of at least 50% in HDRS score in week 5 compared with baseline) and nonresponders were analysed. For analyses of group differences unpaired *t*-tests were used. Discriminant analyses (stepwise procedure using Wilks λ) were performed for Δ2–1 and Δ5–1 in order to explore the separation of the treatment groups on the basis of side effect change score profiles. Significantly discriminating variables were compared jointly by MANOVA based on Wilks λ statistics. Due to the exploratory nature of the study and to reduce type-II errors, the level of significance was set at $\alpha = 0.10$.

Results

Total scorings of undesired effects and somatic complaints (FSUCL total score) showed significant changes during the course of treatment in group TRI (week 1: 10.6 ± 5.6, week 5: 5.0 ± 5.3; paired *t*-test, $t = 5.8$, $df = 13$, $p < 0.0005$), but not in TRI+BLT (week 1: 10.7 ± 4.0, week 5: 8.3 ± 5.9; $t = 1.6$, $df = 13$, $p > 0.10$). However, no significant difference between treatment groups at weeks 1 and 5 was obtained. Furthermore, no baseline differences in single FSUCL item scores could be detected (data not shown). The frequency of patients with emerging specific side effects during acute (week 2) and 4-week treatment (weeks 2–5) is summarized in Table 2 for TRI and TRI+BLT (emergence rates). The baseline rates (week 1, trimipramine treatment; number of patients with scores > 0) are also shown for comparison. Evidently, most of the symptoms assessed by FSUCL occurred frequently in both treatment groups in week 1. No substantial differences in the rate of newly emergent side effects, neither during week 2 nor during weeks 2–5, could be found.

Changes in FSUCL item scores after 1 (week 2) and 4 weeks (week 5) of light treatment and after discontinuation of BLT (week 6) are provided in Table 3 for both groups. Despite comparable numbers of patients with side effects in both groups (TRI and TRI+BLT), significant group differences in change scores could be stated indi-

Table 2 Baseline rates and emergence of side effects (FSUCL) in treatment groups. *FSUCL* Fischer's somatic symptom/undesired effect checklist; *TRI* trimipramine monotherapy (200 mg/d); *TRI+BLT* trimipramine and adjunct bright-light therapy

	Base rates Week 1		Emergence rates Week 2		Emergence rates Weeks 2–5	
	TRI ($n = 14$)	TRI+BLT ($n = 14$)	TRI ($n = 14$)	TRI+BLT ($n = 14$)	TRI ($n = 14$)	TRI+BLT ($n = 14$)
Sedation	10 (71)	11 (79)	2 (14)	0 (0)	2 (14)	0 (0)
Disturbed sleep	12 (86)	13 (93)	0 (0)	0 (0)	0 (0)	0 (0)
Restlessness	11 (79)	11 (79)	0 (0)	0 (0)	0 (0)	0 (0)
Agitation	6 (43)	7 (50)	1 (7)	1 (7)	1 (7)	1 (7)
Disorientation	0 (0)	1 (7)	0 (0)	0 (0)	1 (7)	0 (0)
Miction complaints	2 (14)	2 (14)	2 (14)	1 (7)	2 (14)	1 (0)
Dry mouth	9 (64)	9 (64)	0 (0)	1 (7)	1 (7)	1 (7)
Salivation	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)
Sweating	6 (43)	8 (57)	0 (0)	2 (14)	1 (7)	4 (29)
Impaired accommodation	5 (36)	6 (43)	2 (14)	0 (0)	2 (14)	1 (7)
Decreased appetite	8 (57)	4 (29)	1 (7)	1 (7)	1 (7)	3 (21)
Increased appetite	1 (7)	7 (50)[a]	3 (21)	0 (0)	6 (43)	1 (7)
Stomach pain	2 (14)	5 (36)	0 (0)	0 (0)	2 (14)	0 (0)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)
Constipation	4 (29)	3 (21)	1 (7)	1 (7)	3 (21)	2 (14)
Diarrhoea	1 (7)	0 (7)	0 (0)	1 (7)	0 (0)	1 (7)
Headache	2 (14)	5 (36)	0 (0)	0 (0)	0 (0)	2 (14)
Vertigo	5 (36)	6 (43)	0 (0)	1 (7)	0 (0)	2 (14)
Hypotension	2 (14)	3 (21)	0 (0)	1 (7)	0 (0)	2 (14)

NOTE: Values are numbers (percentages in parentheses) of patients ($n = 14$, each group) with side effects present in week 1 (base rates) or with newly emergent side effects in week 2 or during weeks 2–5 (emergence rates)

[a] Group difference: $\chi^2 = 4.5$, $df = 1$, $p < 0.05$

Table 3 Side effect (FSUCL) and symptom (HDRS) changes in treatment groups

	Acute effects Δ week 2–1		Effects after 4 weeks Δ week 5–1		Discontinuation effects Δ week 6–5	
	TRI (n = 14)	TRI+BLT (n = 14)	TRI (n = 14)	TRI+BLT (n = 14)	TRI (n = 14)	TRI+BLT (n = 14)
Sedation	–0.1 ± 0.6	0.5 ± 1.0[b]	–0.9 ± 0.8	–0.5 ± 0.9	0.0 ± 0.9	0.1 ± 1.0
Disturbed sleep[c,d]	–1.1 ± 0.8	–0.5 ± 1.0	–1.2 ± 0.9	–0.5 ± 0.8[b]	–0.5 ± 0.7	–0.3 ± 0.6
Restlessness[c,d]	–0.7 ± 0.8	–0.2 ± 0.6[a]	–1.2 ± 0.8	–0.5 ± 0.9[a]	0.1 ± 0.5	0.1 ± 0.5
Agitation	–0.2 ± 0.6	–0.5 ± 0.8	–0.5 ± 0.7	–0.6 ± 0.7	–0.1 ± 0.3	0.0 ± 0.0
Disorientation	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0	–0.1 ± 0.3	0.0 ± 0.0
Miction complaints	0.0 ± 0.6	0.0 ± 0.7	0.1 ± 0.5	0.0 ± 0.7	–0.1 ± 0.4	0.0 ± 0.0
Dry mouth	0.5 ± 1.1	0.5 ± 1.1	–0.2 ± 1.0	0.1 ± 1.0	0.0 ± 0.9	0.0 ± 0.8
Salivation	0.0 ± 0.0	–0.1 ± 0.3	0.0 ± 0.0	–0.1 ± 0.3	0.0 ± 0.0	0.0 ± 0.0
Sweating[c]	–0.2 ± 0.8	–0.2 ± 0.9	–0.5 ± 0.8	–0.3 ± 0.6	0.2 ± 0.7	–0.1 ± 0.9
Impaired accommodation	0.4 ± 0.7	0.0 ± 0.8	0.0 ± 0.8	0.2 ± 0.9	0.1 ± 0.4	0.1 ± 0.3
Decreased appetite[c,d]	–0.5 ± 1.2	–0.2 ± 0.8	–0.9 ± 0.9	–0.1 ± 1.0[a]	0.1 ± 0.7	0.1 ± 0.3
Increased appetite[c]	0.4 ± 0.8	0.2 ± 0.8	0.3 ± 0.9	0.0 ± 1.4	–0.1 ± 0.4	–0.1 ± 0.8
Stomach pain	0.0 ± 0.4	–0.1 ± 0.6	–0.2 ± 0.4	–0.3 ± 0.5	0.1 ± 0.5	0.1 ± 0.4
Nausea	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.4
Constipation d	0.2 ± 0.4	0.1 ± 0.7	–0.1 ± 1.0	0.1 ± 0.6	–0.1 ± 0.6	0.1 ± 0.3
Diarrhoea	–0.1 ± 0.3	0.1 ± 0.3	–0.1 ± 0.3	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.3
Headache	0.1 ± 0.5	–0.3 ± 0.5[a]	–0.1 ± 0.3	–0.3 ± 1.0	–0.1 ± 0.3	0.2 ± 0.9
Vertigo	–0.1 ± 0.5	0.1 ± 0.5	–0.5 ± 0.8	0.1 ± 0.9[b]	0.3 ± 0.6	–0.1 ± 0.7[b]
Hypotension[c,d]	–0.1 ± 0.3	0.0 ± 0.4	–0.1 ± 0.3	0.2 ± 0.7	0.0 ± 0.0	–0.1 ± 0.6
HDRS sum score[c,d]	–6.6 ± 6.3	–4.9 ± 4.9	–17.4 ± 7.6	–8.2 ± 8.3[a]	–0.3 ± 4.8	–0.9 ± 5.3

NOTE: Values are mean ± SD of symptom changes (Δ)
[a,b] Differences between treatment groups (TRI vs TRI+BLT, unpaired t-test): [a] $t > 1.7$, $df = 26$, $p < 0.05$; [b] $t > 1.3$, $df = 26$, $p < 0.10$
[c,d] Differences between responders and nonresponders (HDRS, unpaired t-test): [c] Δweek 2–1, $t > 1.3$, $df = 26$, $p < 0.10$; [d] Δweek 5–1; $t > 1.3$, $df = 26$, $p < 0.10$; HDRS responders (improvement > 50% in week 5) showed more favourable changes in all significant differences

Table 4 Results of discriminant analyses

	Δ2–1			Δ5–1		
	TRI	TRI+BLT	p	TRI	TRI+BLT	p
Sedation	–	+	0.02			
Restlessness	–	+	0.05	–	+	0.005
Decreased appetite	–	+	0.006			
Constipation	+	–	0.01			
Impaired accommodation	+	–	0.005			
Sleep disturbance				–	+	0.01
Headache				+	–	0.05
Vertigo				–	+	0.02
MANOVA	$F = 4.3$, $df = 5;20$, $p = 0.008$			$F = 5.1$, $df = 4;21$, $p = 0.005$		

NOTE: Values are signs and p-values of standardized discriminant function coefficients; + increase or weak decrease; – decrease or weak increase of symptoms; the signs are indicative for the respective treatment group; Δ2–1 score differences between weeks 2 and 1; Δ5–1 score differences between weeks 5 and 1. Only significantly ($p \leq 0.05$) discriminating variables are reported. Discriminant analyses were carried out on 10 of 19 symptoms due to omission of variables without considerable between-group variance

cating differences in the perceived intensity (scores 0–3) of side effects. With respect to acute effects (week 2) increased sedation ($p < 0.10$) and improved headaches ($p < 0.05$) could be observed in the group BLT+TRI as compared with TRI, whereas restlessness showed a reduced improvement ($p < 0.05$) in patients on BLT+TRI treatment. After 4 weeks of adjunct treatment, sleep disturbances ($p < 0.10$), restlessness ($p < 0.05$), and decreased appetite ($p < 0.05$) showed less improvement in the group BLT-TRI when compared with patients treated with TRI.

As shown in Table 3, on average group TRI benefitted more than patients treated with TRI+BLT. However,

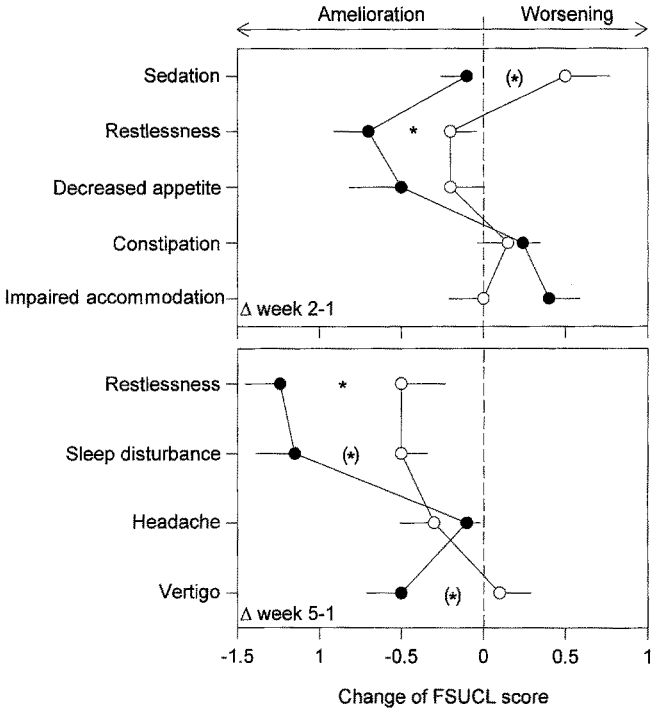

Fig. 2 Change profiles of discriminative symptoms. Values are mean and SEM; *filled circle* trimipramine; *open circle* trimipramine and bright-light therapy; Δ2–1 difference (week 2–1); Δ5–1 difference (week 5–1); (*) $p < 0.10$; *$p < 0.05$ (unpaired t-tests)

HDRS response rates were 11 of 14 (78%) patients for TRI and 6 of 14 (43%) patients for TRI+BLT, respectively. This difference was statistically not significant ($\chi^2 = 2.4$, $df = 1$, $p > 0.10$). Therefore, side effect change scores were descriptively compared between responders ($n = 17$) and non-responders ($n = 11$) of the merged groups to elucidate the dependence of side effect changes on treatment response. Table 3 indicates the FSUCL change scores with significant differences between HDRS responders and non-responders and shows that changes in sedation, headache and hypertension were not dependent on treatment response. Table 4 yields results from discriminant analyses for changes between week 1 and week 2 (Δ2–1) or week 5 (Δ5–1), respectively. Items without substantial between group variance were omitted; only clearly discriminating items ($p \leq 0.05$) are presented.

Both discriminant functions were statistically significant (Δ2–1: Wilks $\lambda = 0.48$, $df = 5$, $p = 0.008$; Δ5–1: Wilks $\lambda = 0.51$, $df = 4$, $p = 0.005$). On the basis of the discriminant functions allocation to treatment groups was possible with 85% accuracy (Δ2–1 and Δ5–1); sensitivity (group BLT) reached 92 and 69%; specificity reached 77 and 100%, for Δ2–1 and Δ5–1, respectively.

The discrimination of both treatment groups according to changes in side effects yielded different profiles of side effect changes for acute and 4-week effects (Fig. 2).

Discussion

The present study shows that the combination of an antidepressant drug with bright light results in a different side effect profile compared with drug monotherapy. However, adjunct bright light did not evoke additional severe symptoms in major depressive patients and is therefore considered to be safe.

Taking into account baseline scores of depressive symptoms and side effects due to standard treatment with a tricyclic antidepressant drug, the evaluation of additional bright-light effects is apparently confounded. Dry mouth, sweating, disturbance of accommodation, vertigo and sedation were predominating side effects during the baseline treatment with trimipramine. These findings are in line with other studies and might be primarily attributable to anticholinergic mechanisms [5]. Furthermore, sleep disturbance, restlessness, agitation and decreased appetite occurred in a substantial proportion of patients as part of their depressive syndrome. The acute effects of intensive BLT applied daily for 1 week did not lead to a substantial further emergence of specific side effects. An augmentation of antidepressant efficacy, however, also did not occur, although from studies in SAD patients a gradual improvement during 1 week of BLT could have been expected [26].

The lack of further improvement could be due to several factors, e.g. different biological or sociodemographic conditions of the two groups despite random assignment [7]. Although similar numbers of patients with or without specific side effects were found in both treatment groups, moderate but reliable differences in the perceived severity of side effects emerged. More complicated is the fact that side effects of bright light seem to be covered by delayed improvement of particular symptoms of depression such as restlessness, sleep disturbance and decreased appetite. These symptoms showed faster and more pronounced improvement in treatment responders. Our results therefore suggest a partial dependence of side effects on the treatment outcome notwithstanding results from a previous study [15]. Discriminant analyses [20] revealed patterns of symptom changes separating the treatment modalities.

Accentuated sedation, ameliorated constipation and accommodation problems during acute adjunct BLT (week 2) showed no relationship to treatment outcome. This finding points to specific properties of BLT. Despite the significant discriminating power of these variables, only the group difference in sedation reached significance indicating distinct but mild effects. Increased sedation and delayed improvement of subjective sleep disturbance during additional BLT was unexpected: according to the hypothesized phase-delaying properties, evening bright light should improve morning sleep and reduce sleepiness the following day [13]. However, the limited empirical evidence from studies using evening light revealed also the occurrence of disturbed sleep in 5 of 8 SAD patients [12]. After 4 weeks of adjunct therapy, reduced complaints about headache but aggravated vertigo occurred indepen-

dently of treatment course. As regards the latter, improvement after discontinuation of BLT was found; the amelioration of headache under BLT partially conflicts with previous reports [8, 15, 18]. In one study [15], however, remission of headache occurred in 28% of patients as opposed to an emergence of the symptom in 19% of patients.

A major difference between this and previous studies is that in our clinical study all patients started with a tricyclic anti-depressant treatment. Thus, base rates of symptoms due to side effects were much higher than expected for untreated patients and improvement of symptoms was more probable due to ceiling and regression effects. However, as depressive illness comprises a variety of symptoms and sub-syndromes, including somatic complaints, and vegetative symptoms, expected side effects of antidepressants could interact with response in different ways: antidepressants or combinations could result in 'positive' side effects (e.g. activation in retarded patients, sleepiness in sleepless patients), thus becoming desired effects.

On the other hand, the emergence of side effects which are components of illness symptomatology may cause worsening of the illness course. That bright light may cause dramatic changes in affective state was demonstrated in studies on SAD patients, as some patients developed hypomanic or manic states after exposure to BLT [8, 12, 18]. From the present study there is no evidence for such adverse effects of adjunct bright light in MDD patients. However, the group treated with adjunct BLT comprised only 2 patients with bipolar disorder (DSM-III-R 296.5). Additionally, delayed recovery from depression due to other factors, (baseline severity, biological variables, sociodemographic parameters) may be associated with delayed improvement in somatic complaints [7]. These influences could be confounded with the side effects of either treatment and it seems impossible to disentangle such relationships in our naturalistic study. Nevertheless, the relatively rare and mild side effects attributable to adjunct BLT resulted in a characteristic alteration in the side effect profile of the tricyclic antidepressant trimipramine with both positive or ameliorating and worsening or aggravating aspects. Interpretation of the present results should, however, take into account that a relatively high intensity of BLT was used. Whereas augmenting light intensity has been proposed to provide greater benefit [25], results of a previous study [15] indicated no relationship between side effects and intensity of light used. As a further limitation, the present study used no additional placebo or sham treatment condition. Although in the case of BLT an accurate double-blind condition cannot be achieved, no differences between bright and dim light conditions (50 vs 2500 lux) could be found with respect to emerging side effects [30]. However, as no previous study has evaluated side effects of combined pharmacotherapy and BLT, the question as to which side effects of adjunct BLT were definitely attributable to bright light remains unclear.

Since the mechanism of action for BLT in depression still needs to be unraveled, it can only be speculated about underlying mechanisms leading to the observed side effect changes: the pattern of specific acute side effect changes of combined TRI+BLT therapy comprising increased restlessness, decreased appetite as well as ameliorated constipation and accommodation problems is tentatively in line with a serotonergic mechanism of BLT as proposed by Rao et al. [20]. These authors found substantially elevated blood serotonin profiles after phototherapy in healthy subjects and in MDD patients, however, without reporting side effects or symptom changes.

This could also explain why BLT led to a specific change of pre-existing side effects of TRI therapy and suggests the evaluation of side effect profiles as an additional clinical tool for research in BLT. The results are in need of replication with larger sample sizes and using a placebo condition (dim light). In keeping with the literature, adjunct bright light can – with respect to the restrictions of the present data – be regarded as safe. However, prior to including adjunct light therapy routinely in treatment programs of non-seasonal MDD, the efficacy has to be verified, and further studies investigating potential side effects of combined treatments are indispensable.

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