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ORIGINAL PAPER

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Is the antidepressive effect of sleep deprivation stabilized by a three day phase advance of the sleep period?

A pilot study

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Abstract Sleep deprivation (SD) induces a rapid amelioration of mood in about 60 % of depressed patients. After the next night of sleep, however, most patients experience a relapse. Previous studies demonstrated that a six day sleep-phase advance protocol prevents relapses in about 60 % of patients who responded positively to SD. We investigated whether also a three day phase advance of the sleep period might be able to maintain the antidepressant effects of SD. Twenty-eight medicated depressed inpatients, who had a significant improvement after a SD in one night were recruited for this study. The phase advance protocol began on the first day after SD with a bed time from 5:00 p. m. to 12:00 p. m. on the first, from 7:00 p. m. to 2:00 a. m. on the second and 9:00 p. m. to 4:00 a. m. on the third day after SD. Three patients dropped out because of protocol violations. Only ten of the remaining 25 SD responders had a relapse during the three days of phase advance treatment or during the two days after it. Two of the relapsers improved again until day 6, i. e. 68 % showed an improvement of at least 30 % six days after the beginning of the treatment. This study indicates that even a three day phase advance protocol may help to prevent relapses after successful SD.

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Introduction

For over 30 years, a one night SD has represented a biological treatment for depressive disorders (for overviews see Van Hoofdakker 1997 and Wirz-Justice & Van Hoofdakker 1999). Wu and Bunney (1990) have reviewed from more than 60 clinical trials: 59 % of the patients show a marked decrease of their depressive symptoms the day after a night of total SD. Also partial SD in the second half of the night may induce an improvement of mood which is comparable to that of total SD in one night (Sack et al. 1988). Since most patients, however, relapse after the next night of sleep, the clinical utility of the treatment is essentially limited (Wu & Bunney 1990). More sustained antidepressant effects have been reported when combining SD with medication, such as, lithium (Grube & Hartwich 1990, Benedetti et al. 1999) or pindolol (Smeraldi et al. 1999), or with light therapy (Neumeister et al. 1996, Colombo et al. 2000). Another strategy is the serial administration of a partial SD once or twice a week (Kuhs et al. 1996, 1998).

It has been shown in several clinical trials that a "phase advance" of the sleep period after SD can prevent relapses in about 60 % of responders to SD (Souetre et al. 1987, Vollmann & Berger 1993, Riemann et al. 1996, Berger et al. 1997, Albert et al. 1998). The rationale behind the combination of SD with a consecutive phase advance is based on studies comparing partial SD during the first and the second half of the night (Wehr 1990 for overview) and on "nap" studies after SD in depressives (Wiegand et al. 1987, Riemann et al. 1993). These studies indicate that sleep negatively affects the mood of depressed patients or may induce relapses after successful SD, especially when sleep falls into a critical phase from early morning until noon. Advancing the sleep period prevents sleep during this critical time and was therefore assumed to minimize the risk of relapses after successful SD.

A matched controlled study in unmedicated, depressed patients compared the effects of SD and consecutive sleep phase advance with the effect of SD and a consecutive sleep phase delay (Riemann et al. 1999). The advance protocol was significantly superior to the delay protocol to stabilize the antidepressant effects of SD (75 versus 40 % responder, respectively). As this procedure, however, needs much time and effort for the staff and high motivation by the patients, in the present study we tested whether a curtailed protocol with only three days of sleep phase advance might be sufficient to prevent relapsing after a successful SD in depressed patients.

Recently, Benedetti et al. (2001) reported that a three day sleep phase advance could sustain the acute antidepressant effect of total SD in one night in a group of bipolar depressed inpatients. Half of the patients were devoid of psychotropic medication, the other half were on chronic lithium salts treatment. The authors described better clinical effects in the lithium-treated group and concluded that the phase-delaying effect of lithium on biological rhythms may have caused a better synchronization of biological rhythms with the sleep-wake cycle.

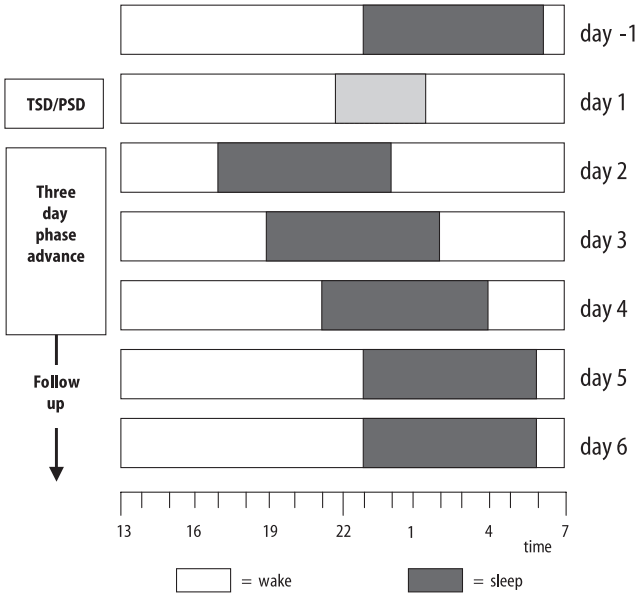

Fig. 1 Treatment protocol of sleep deprivation and a consecutive 3-day phase advance of the sleep period. Daily ratings were continued during a follow-up until day 6 in order to observe the stability of the antidepressant effect. *TSD* total sleep deprivation; *PSD* partial sleep deprivation

Methods and patients

This open pilot study was conducted at the departments of Psychiatry and Psychotherapy of the Universities of Freiburg, Tuebingen and the Technical University of Munich. Informed consent was obtained by all patients prior to inclusion. The study protocol was approved of by the ethical committee of the medical faculty of the University of Freiburg.

Inclusion criteria were a current major depressive episode according to ICD-10 criteria, unipolar or bipolar, and a positive response to SD. This was operationalized as an at least 30 % reduction of depressive symptoms compared with the day before SD, measured by a modified HAMD scale with only 6 items (depressed mood, guilt feelings, work and interest, psychomotor retardation, anxiety and physical symptoms, maximum score 22, Bech et al. 1975). Exclusion criteria were suicidality, secondary depression as a consequence of a somatic disorder or a severe physical disorder. All patients had either a total SD in one night (TSD, n = 21) or a partial SD in the second half of the night (PSD, n = 7). On the day after the sleep deprived night, they then underwent a consecutive three day phase advance treatment (Fig. 1), i. e., bed time was restricted to 5.00 p. m. until 12.00 p. m. on the first day after SD, to 7.00 p. m. until 2.00 a. m. on the second day, and to 9.00 p. m. until 4.00 a. m. on the third day after SD. After that, patients were allowed to sleep between 11.00 p. m. and 6.00 a. m.

Twenty-eight patients fulfilled the inclusion criteria and entered the trial after giving their informed consent. Three patients had to be excluded from the analysis because of protocol violations, i. e., their sleeping and waking periods did not correspond with the advance protocol in at least one of the nights. The demographic data of the remaining 25 patients are shown in Table 1. Twenty-four patients were additionally treated with antidepressants. Five were kept on a low dose of benzodiazepines throughout the trial. Most of them had been on a stable medication for four or more weeks prior to inclusion into the trial. None of the patients had been treated with SD and sleep phase advance prior to inclusion. From day –1 until day 6, ratings were performed every morning using the 6-item version of the HAMD scale. For daily self-ratings of mood, the adjective mood scale (AMS, maximum score = 56, von Zerssen 1986), was completed daily from day –1 until day 6. Patients who maintained a reduction of the 6-item HAMD scores of at least 30 % following the phase advance protocol on day 4 were classified as responders to treatment. The other patients were classified as relapsers.

For statistical analysis, means and standard deviations were calculated. For the HAMD and AMS values of days –1 through 6 general linear models with repeated measurements were calculated, also for the HAMD and AMS values of days 1, 4 and 6. Greenhouse Geisser adjustment was administered when Mauchly Sphericity Test reached significance. The level of significance was set at $p < 0.05$, for multiple testing Bonferroni adjustment of the level of significance was performed. The corrected α-values were $\alpha^* = 0.0253$ for 0.05 and $\alpha^{**} = 0.0050$ for 0.01.

Results

Twenty out of the 25 SD responders (80 %) maintained their improvement until day 4 after the sleep phase advance therapy, demonstrated by a reduction of the HAMD scores of at least 30 %. Most of the patients also maintained this improvement during a two day follow-up after the end of the advance protocol. Five out of 20 patients relapsed, and two out of 20 improved during this period. On day 6, 17 out of 25 patients (68 %) showed an improvement of at least 30 % compared with the baseline. Of the five patients who did not maintain their improvement after SD, two relapsed on day 2, two on day 3 and one on day 4. Based on an "intention to treat" approach, 60.7 % were classified as responders. The results were comparable in all centers.

As shown in Fig. 2, the mean 6-item HAMD scores decreased from 10.4 ± 3.0 to 4.1 ± 2.6 ($p < 0.000$ vs. baseline) the day after SD and remained on a markedly improved level until day 4 after the end of the advance treatment (4.5 ± 3.1, $p = 0.002$ vs. baseline). The therapeutic effect was also stable at a follow-up on day 6 (5.5 ± 3.9, $p = 0.000$ vs. baseline). The stabilizing effect of the phase advance treatment after SD was also con-

Table 1 Demographic variables of patients

	All patients	Responder (day 6)	Non-Responder (day 6)	t-test (Resp. vs. Non-Resp.)
N	25[a]	17	8	
Age (in years, mean ± SD)	53 ± 11.9	56.7 ± 10.9	45.1 ± 10.51*	p = 0.020
Female/male	12/13	8/7	4/4	
HAMD-score (21 items, mean ± SD)	23.6 ± 6.6	23.7 ± 6.9	23.5 ± 6.2	p = 0.944
Duration of episode (in weeks, mean ± SD)	44.3 ± 39.2	49.3 ± 42.1	33.5 ± 32.0	p = 0.357
Number of depressive episodes	6.0 ± 9.5	4.9 ± 7.6	8.1 ± 4.9	p = 0.446
Total duration of illness (in months, mean ± SD)	91.3 ± 106.4	78.1 ± 99.2	119.3 ± 122.5	p = 0.378
Unipolar/bipolar	22/3	15/2	7/1	
Diurnal variations of mood yes/no	24/1**	16/1**	8/8	
Antidepressants*:	24	16/1	8/0	
TCA	19	9	7	
SSRI	7	5	2	
SNRI	2	2	–	

[a] 12 patients were treated in Freiburg, 6 in Munich and 7 in Tuebingen
* few patients had a combination of two antidepressants
** in almost all patients "positive" mood swings
TCA tricyclic antidepressants; *SSRI* selective serotonine reuptake inhibitors; *SNRI* serotonine noradrenaline reuptake inhibitors

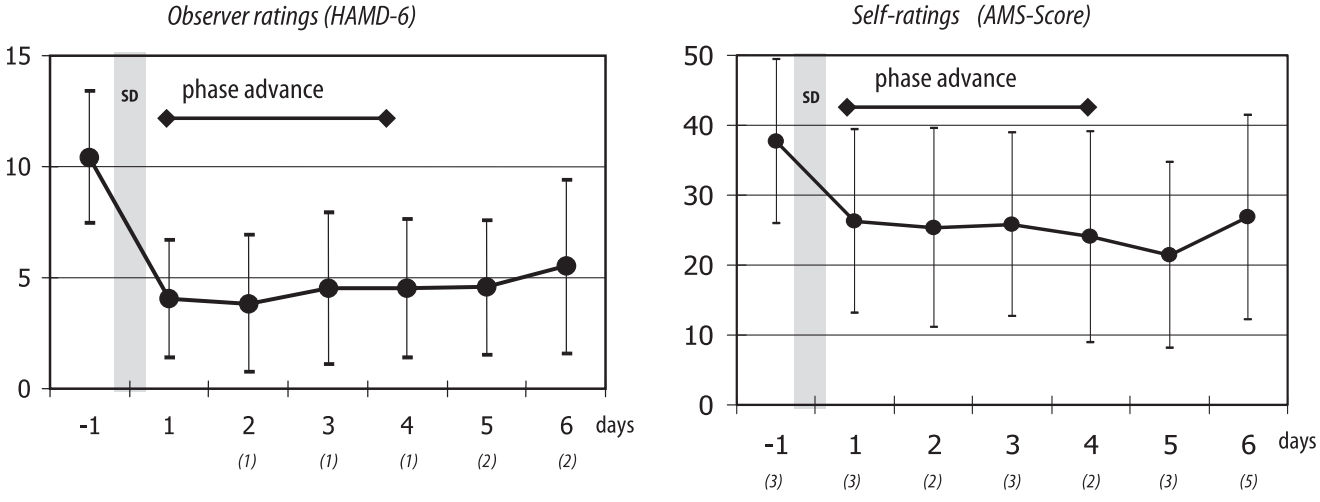

Fig. 2 Impact of SD and consecutive sleep phase advance over 3 days on depressed mood in 25 inpatients. Means ± standard deviations of the 6-item HAMD scale and AMS (= Adjective mood scale) from day −1 until day 6. The number of missing rating scales are given in parenthesis. *SD* Sleep deprivation. Statistical evaluation by ANOVA for repeated measurements (df = 1) showed significant effects for both observer and self-ratings (p = 0.000, p = 0.000, respectively). When calculating contrasts between days 1, 4 and 6 and day −1, the improvement was significant at the p < 0.01 level (Bonferroni-corrected) on all days for both the HAMD-6 and the AMS score

firmed by self-ratings (p = 0.000, p = 0.005, Fig. 2). No major adverse events were observed during the treatment.

In the comparison of the 17 patients who improved by at least 30 % on day 6 with the eight patients who had not maintained their improvement, no statistically significant differences were found either for the 21-Hamilton Depression ratings before treatment, for the duration of the illness and the current episode, or for the number of depressive episodes. Furthermore, no gender differences between the group of responders and non-responders were found. The only difference observed was related to age, since responders to the treatment were significantly older than non-responders (p < 0.05).

Discussion

Our results confirm earlier findings demonstrating that a phase advance treatment is able to stabilize the improvement after an antidepressant SD. In this study, 80 % of the patients improved by at least 30 % at the end of the

treatment. Only five more patients relapsed within the two days following the advance protocol, whereas two improved again, i. e., 68 % maintained their improvement on day 6 after sleeping at usual times.

In contrast, it is well known that relapses almost regularly occur when depressed patients sleep at a usual time after an antidepressant SD.

Surprisingly, the response rates with a 3-days advance protocol were similar to those in earlier studies using a 6-days phase advance treatment after SD (Vollmann & Berger 1993, Berger et al. 1997, Albert et al. 1998, Riemann et al. 1999). This is in agreement with a recent study by Benedetti and coworkers (2001) who investigated 30 depressive patients with SD and consecutive 3-days phase advance and found that phase advance was able to sustain the antidepressant effect of SD.

It has to be emphasized that there was no control group in this trial. A placebo effect can therefore not be excluded. Up to now, there is only one study comparing the antidepressant effects of a phase advance treatment with a control group participating in a phase delay protocol (Riemann et al. 1999). In both groups the treatment began with a SD. Psychotropic medication was not allowed. In the advance group, 76.5 % of those patients who had an at least 50 % improvement sustained their 50 % response until the end of the advance protocol compared to only 31 % in the delay group. Since in this controlled trial the patients were blind with respect to the study hypothesis, a placebo phenomenon was unlikely to be the reason for such positive results of several earlier uncontrolled trials.

In the present study nearly all patients received antidepressants; however, most had been refractory to drug treatment for four or more weeks. In this trial, the mean decrease in HAMD 6-item ratings was 57 % after 4 days and still 47 % after 6 days. Such an improvement within few days clearly exceeds the effects being observed with antidepressants alone. Therefore, the therapeutic results of this trial cannot be explained by concomitant antidepressant drug treatment.

We compared responders and non-responders to treatment with regard to the clinical characteristics possibly predicting the response to the treatment. The only difference was in the age of the patients, since it was significantly higher in the group of responders. The sample was small and consisted only of patients who already showed an antidepressant response to SD and almost all had daily mood swings. Whether patients without a therapeutically successful SD would also respond to a sleep phase advance cannot be answered since no studies have been performed including SD non-responders. The impact of the age on the outcome is a preliminary finding which must be confirmed by larger studies.

Compared with earlier studies using a six day advance protocol, this pilot study indicated that advancing the sleep time for three days suffices to maintain the antidepressant response to SD. These promising results should be confirmed by further studies with larger sample sizes and by including a control group. The combination of TSD or PSD with a consecutive sleep advance therapy might be superior to a conventional SD therapy with regard to the duration of the antidepressive effect. In patients with major depressive episodes it might be especially helpful during the first weeks of antidepressant drug treatment because of the well-known delay of their onset of action. The curtailed three day advance protocol is also more practicable for both patients and nurses than the former six day procedure.

The mechanism of action of the procedure has to date not been understood. It has been postulated that endogenous circadian rhythms are phase advanced in depressive patients (Wehr et al. 1979). Advancing the sleep-wake-rhythm (without prior partial or total SD as in our protocol) was therefore assumed to have an antidepressive effect due to a synchronization of sleep and endogenous circadian rhythms. In fact, several small and uncontrolled studies (see Wehr 1990 for overview) have indicated a mood-improvement of depressed patients after an advance-shift of their sleep-wake rhythm. The assumption of phase-advanced circadian rhythms was not proven, however, since 24-hour measurements of temperature or cortisol did not consistently show abnormalities of the circadian rhythmicity (Sack et al. 1987). One of our earlier hypotheses was based on the well-known REM sleep abnormalities of patients with depression such as a shortened REM latency (Wichniak et al. 1999, for overviews see Benca et al. 1992 and Riemann et al. 2001). It was postulated that SD and sleep phase advance have an antidepressant effect because they may lead to a normalization of these abnormalities. However, sleep laboratory investigations of unmedicated depressive patients who underwent SD and sleep phase advance therapy failed to prove any suppressive effect on REM sleep parameters (Riemann et al. 1999).

In healthy humans, SD influences many biological functions such as endocrinological systems (see van Cauter 2000) and immunological functions (Heiser et al. 2000, Dinges et al. 1995 for overview). In depression, SD has a variety of neurobiological effects including findings of functional brain imaging. This indicates that SD induces similar effects in the CNS as psychostimulant drugs do (see Ebert & Berger 1998 for overview). The antidepressive effect of SD may therefore be mediated by the acute neuroendocrinological and neurotransmitter changes brought about as a reaction to sleep loss. Whether sleep phase advance alone in a similar vein may have a psychostimulant effect is questionable, since studies measuring neurochemical or neuroendocrinological parameters or brain imaging during this type of treatment have not yet been undertaken. The precise mechanism of action therefore remains unknown.

In summary, this pilot study indicates that the combination of SD in one night with phase advance of the sleep period for the following three days has a sustained antidepressive effect. However, these results must be confirmed by controlled studies.

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