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How to preserve the antidepressive effect of sleep deprivation: A comparison of sleep phase advance and sleep phase delay

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Abstract Total sleep deprivation (TSD) leads to an immediate amelioration of depressed mood in approximately 70 % of patients with the melancholic subtype of depression. The clinical utility of this procedure is limited, as the improvement usually subsides after the next night of sleep. In the present study, 40 depressed inpatients, being free of psychoactive medication for at least 7 days and who had responded to a TSD were then distributed (according to a matched-pair design) to a sleep phase advance (SPA = time in bed scheduled from 1700–2400 hrs) or a sleep phase delay (SPD = time in bed from 0200–0700 hrs) with a succeeding shift back (for one hour in the SPA group per day) respectively shift forward (for 30 minutes in the SPD group per day), until the initial sleep phase (2300–0600 hrs) was reached after seven days again. Based on previous observations it was hypothesized that a phase advance of the sleep period should prevent responders to TSD from relapsing. Whereas 75% of the TSD responders were stabilized by the phase advanced condition and did not relapse over a period of seven days, only 40% of the patients in the phase delayed condition did not relapse. Polysomnography during the course of the study gave no evidence that the unusual sleep schedules caused prolonged sleep deprivation. Abnormalities of REM sleep persisted both in the clinical responders and non-responders after the sleep wake manipulation. It is concluded that the clinical effectiveness of TSD can be significantly improved by combining TSD with a following phase advance of the sleep period.

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Introduction

Total sleep deprivation (TSD) leads to a swift improvement of mood in approximately 70% of patients suffering from major depressive disorder (MDD). Unfortunately, in more than 80% of unmedicated TSD responders a relapse into depression occurs after the next night of sleep [29] or even after brief naps [27].

As to the mechanism of action of TSD, several hypotheses were proposed including chronobiological and neurochemical models having in common that TSD interferes with a sleep-dependent depressiogenic substance or processes, or augments a wake-dependent antidepressant substance or process [see 21, 29].

Several efforts have been undertaken to prolong the short-lived antidepressant effect of TSD, including concomitant antidepressant medication [11] or light therapy [14]. Our own work in this area has been devoted to a phase advance (SPA) of the sleep period following TSD. This approach is based on the hypothesis that especially sleep after midnight and in the morning hours possesses depressiogenic properties. This hypothesis is founded on the following observations: After successful sleep deprivation brief naps in the morning, in contrast to naps in the afternoon, reverse the TSD effects [28]. In addition, an improvement of depression was shown in four previous investigations with a phase advance (for five to six hrs) of the sleep period over 14 to 21 days [18, 19, 22, 26]. Thirdly, partial sleep deprivation in the second half of the night is superior to partial sleep deprivation in the first half of the night [12, 17]. The latter two observations stimulated Wehr et al. already in 1979 to formulate the "internal coincidence" hypothesis [24–26], postulating a "critical time zone" in the early morning hours, which seems to constitute a vulnerable time for relapses into depression when sleep takes place.

To empirically validate our concept, we performed trials of TSD followed by seven days of SPA, starting with a scheduled time in bed from 1700–2400 hrs and then a daily shiftback of time in bed for one hour, until after seven days the conventional time in bed from 2300–600 hrs was reached. In two pilot studies [5, 23], it was shown that combined TSD & SPA kept 2/3 of TSD responders from relapsing into depression during the ensuing week after TSD, in contrast to only 10–20 % retaining remission with a normal sleep schedule [16, 29].

In the present study we circumvent methodological pitfalls of our pilot studies by including a control group (sleep phase delay – SPD) and postulated that:

- TSD combined with SPA is clinically superior to TSD with SPD,
- no consecutive sleep deprivation occurs during SPA as documented by polysomnography.

Material and methods

Sample

The "intent to treat" population consisted of 57 psychiatric inpatients with a primary major depressive disorder (51 unipolar, 6 bipolar), according to DSM-III-R criteria, who were admitted to both departments (Freiburg and Göppingen). Patients were free of any serious somatic disorder. Mean age (± SD) of the whole sample was 42.3 ± 12.8 yrs. Forty-four of the patients (77.2 %) responded to TSD (criteria see below) and were distributed to consecutive SPA or SPD (Psychopathological data of ten of the SPA patients have already been included in: Am. J. Psychiatry 154 (1997) 870–872). Twenty patients in each group could be matched with regard to age and severity of depression (see Table 1).

Patients in the SPA condition did not differ from SPD patients concerning any of the listed variables. Prior to inclusion in the study, all patients were informed in detail about the experimental procedures – but were kept blind to the hypothesis that SPA is superior to SPD – and gave informed written consent. Patients were assured that they could terminate the study any time. The study had been approved by the local ethical committee.

Design

Only patients free of any kind of psychoactive medication for at least 7 days (fluoxetine and neuroleptics: 21 days) prior to the beginning of the study were included. Depressed patients with acute suicidal or psychotic features were excluded. All patients slept two nights in the sleep laboratory prior to TSD. The first night was meant for adaptation, the second for collecting baseline data. After these sleep recordings, patients were subjected to a trial of TSD. During this time patients were under constant observation by a nurse to prevent napping. During the night patients were engaged in activities like watching TV, playing table tennis or other games.

The decision as to whether or not a patient had responded to TSD was made after the 1600 hrs 6-HAMD rating on the day following TSD (day 3). Patients were distributed to the two experimental conditions by a matched-pair approach. Criteria for matching were age, severity of depression, and response to sleep deprivation (see below). SPA started with a time in bed from 1700 to 2400 hrs (after 35 hrs. of prior wakefulness) and then time in bed was shifted back for one hour each day until after six days the usual time in bed from 2300 to 0600 hrs was reached. SPD started with a time in bed from 0200 until 0900 hrs (after 44 hrs. of prior wakefulness) and then was shifted forward for 30 min. daily until after six days the usual bedtime was reached. The SPD condition thus was not exactly the "mirror image" of SPA. Our primary aim when designing the study was to compare an experimental condition avoiding sleep (= SPA) during the "critical time zone" [25], with a condition allowing sleep during that time period (= SPD). An initial 6 hour shift also in the delay condition would have implied a total period of 47 hours of sleep deprivation and a bed time between 0500 hours and 1200 hours in the first night of SPD. This procedure did not seem to be acceptable for the patients and would have prevented sleep also during the second half of the night.

All patients slept in the sleep laboratory during the whole study. If patients could not fall asleep during phase shifting, 7.5 mg Zopiclone was offered.

Depression ratings

The 21-HAMD rating scale was performed prior to the first investigation in the sleep laboratory and patients were required to have a score ≥ 18 to be eligible. The 21-HAMD was repeated on the day before TSD (day 2) and after the last shifted sleep time (day 10), or in case of premature termination of the study at the day of termination.

The 6-HAMD was used to measure depressive mood daily throughout the entire study at 0900 and 1600 hrs by experienced raters. The 6-HAMD is an abbreviated version of the 21-HAMD and has a maximum score of 22 pts, excluding the sleep and diurnal variation items. It is a psychometric instrument suitable for repeated measurements [2]. All rating interviews were videotaped, time cues were eliminated and a subsample of ratings (n = 30) was re-analyzed by an independent rater. Comparison of the original scores with the re-analysis documented a high concordance of ratings with a correlation coefficient (product-moment correlation) of r = 0.92 ($p < 0.001$).

Table 1 Description of samples

	Sleep phase advance (N = 20)	Sleep phase delay (N = 20)	t-Test (two-tailed) df = 38	
			t =	p =
Age	46.0 ± 9.5 yrs	43.7 ± 13.3 yrs	0.63	0.532
Male/female	8/12	11/9	0.90	0.342[1]
21-HAMD	29.1 ± 5.0	26.3 ± 5.9	1.65	0.107
Uni-/bipolar	18/2	16/4	0.78	0.375[1]
Number of depressive eposides	2.9 ± 2.4	6.7 ± 9.8	–1.63	0.112
Total illness duration	7.6 ± 9.3 yrs	8.6 ± 9.3 yrs	–0.33	0.740
Duration of current episode	25.4 ± 60.2 weeks	22.5 ± 26.3 weeks	0.19	0.847
Diurnal variation (yes/no)	15/5	15/5	0.00	1.000[1]

[1] Chi-square test statistics are given

Response criteria

TSD response was defined as at least a 30% improvement of the 6-HAMD values (averaged 0900/1600 hrs values) comparing ratings on the day prior to TSD to the day following TSD. Response to SPA or SPD was defined as a persistence of an at least 30% reduction on the 6-HAMD on the last day of the study compared to pre-TSD levels. An additional data analysis set the response criterion for TSD and SPA/SPD to ≥ 50% improvement on the 6-HAMD.

Polysomnography

Sleep EEG recordings were performed and scored according to standard procedures [15]. In the present report target variables of sleep include sleep efficiency (the ratio of total sleep time to time in bed × 100%), Slow Wave Sleep % SPT (SPT = Sleep Period Time, i. e., the time from sleep onset until the last sleep stage during the record), REM % SPT and REM latency (the time from sleep onset, i. e., the first occurrence of sleep stage II, until the first occurrence of stage REM).

Statistics

For descriptive purposes, means and standard deviations (SD) were calculated. For inferential statistics mainly parametric methods were used including analysis of variance (ANOVA) and T-tests. For dichotomous variables (response/non-response) the Chi-Square Test was used. To deal with the problem of premature drop-outs and ensuing reduced N, the LOCF method (Last Observation Carried Forward) was used for psychopathological data, but not for sleep EEG data.

The level of significance was set at $p < 0.05$. One- or two-tailed levels of significance were applied, depending on whether or not the hypothesis tested was directed.

Results

Response to TSD

Forty-four (77.2%) of the 57 included patients showed a positive response to TSD as defined by our criteria and were matched in order to participate either in the SPA or SPD procedure. Two patients from each experimental condition were excluded from the data analysis though they completed the full trial in order to keep the groups comparable with respect to initial severity of depression. This resulted in 20 patients in each experimental condition, who were indistinguishable concerning age, severity of depression and other demographic or psychopathologic variables (see Table 1). Though all 40 patients were TSD responders according to our 30% response criterion, TSD response was weaker in the SPD group compared to the SPA group. Mean 6-HAMD in the SPA group decreased from 9.5 (SD: 2.8) to 2.6 (SD: 2.0), whereas in the SPD group mean 6-HAMD was reduced from 9.4 (SD: 3.4) to 4.4 (SD: 2.5). Pre-TSD values were indistinguishable (p = 0.960, df = 38, T = 0.05, two-tailed T-Test), but post-TSD values differed significantly (p = 0.017, df = 38, T = –2.49, two-tailed T-Test).

Therapeutic response to SPA/SPD

Drop outs

Eight of 40 patients (20%) did not stay in the study until final completion. In all cases premature termination of the study was related to non-response to the phase shift of sleep. In the SPA group one patient dropped out (day 6). In the SPD condition seven subjects did not fully complete the study. Two subjects dropped out on day 5, three patients on day 6, and one subject each on day 8 and on day 9. Comparing drop-out rates between SPA (5%) and SPD (35%), a p-value of 0.044 was achieved (Chi-Square Test, two-tailed).

Dichotomous response criteria

In the next step of data analysis therapeutic response to SPA/SPD was compared according to the maintenance of an at least 30% improvement on the 6-HAMD as a criterion for therapeutic response (LOCF method). With this criterion 15 patients in the SPA group (75%) and eight patients in the SPD group (40%) were therapy responders (p = 0.027; Chi-Square test, one-tailed).

Applying a more strict 50% criterion for response to TSD and phase shifting, 17 patients in the SPA condition as compared to 13 patients in the SPD condition were considered TSD responders. 13 of the 17 SPA patients sustained their 50% response throughout the study vs. four out of the 13 SPD patients (p = 0.015, Chi-Square Test, one-tailed).

When matching patients of both groups exactly according to TSD response, 12 patients were retained in each group. Improvement due to TSD was then indistinguishable (SPA: 63.5%, SD: 15.2; SPD: 65.6%, SD: 15.5; p = 0.744, df = 22, T = –0.33, two-tailed T-Test) but % improvement at the end of the study differed significantly (SPA: 67.1%, SD: 30.7; SPD: 33.5%, SD: 38.9; p = 0.015, df = 22, T = 2.34, two-tailed T-Test).

Longitudinal data

Data analysis of 6-HAMD ratings with a two-factorial ANOVA, the factors being repeated measurement (starting with pre-TSD until the last day of the study = 9 measurements), experimental condition (SPA versus SPD) and interaction was applied.

For repeated measurements a $p < 0.001$ was observed (F = 22.83, df = 8, 304), the factor experimental condition yielded a p = 0.042 (F = 4.41, df = 1, 38) and for the interaction factor a p = 0.068 was determined (F = 2.2, df = 4.1, 304 corrected according to Greenhouse-Geisser).

Looking at the percent improvement observed between the first and last day of the study on the 6-HAMD, mean improvement was 60.0% in the SPA group compared to 25.5% in the SPD group (p = 0.025, df = 38, T = 3.01, T-Test, one-tailed).

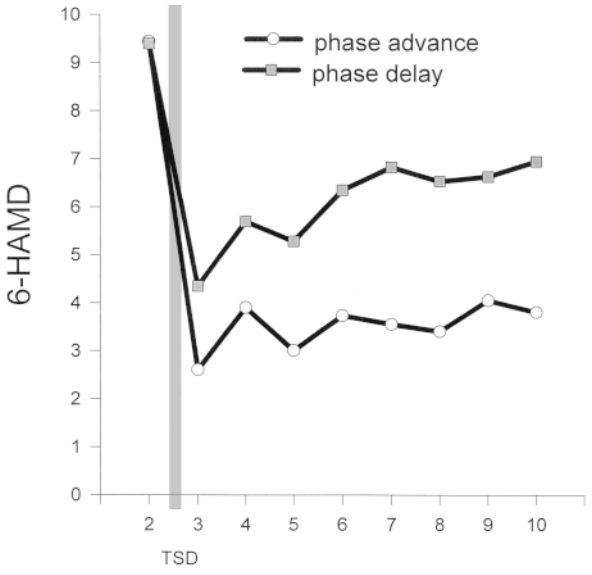


Fig. 1 Mean values of 6-HAMD for SPA and SPD group

Initial 6-HAMD was 9.5 (SD: 2.8) in the SPA group compared to 9.4 (SD: 3.4) in the SPD group (Test statistics see above). At the end of the study values were significantly lower in the SPA group (3.8 ± 4.4) compared to the SPD group (7.0 ± 4.9) (p = 0.016, df = 38, T = –2.15, T-Test, one-tailed).

21-HAMD data

This scale was applied two times, i. e., at day 2 and after termination. Scores in the SPA group decreased from 29.1 (SD: 5.0) to 11.8 (SD:10.1), whereas in the SPD group the 21-HAMD decreased from 26.3 (SD: 5.9) to 17.5 (SD: 12.1). A two-factorial ANOVA, with the factors being repeated measurement and group (SPA vs. SPD) revealed a $p < 0.001$ (F = 71.1, df = 1, 38) for repeated measurement, a $p = 0.547$ for the factor group (F = 0.4, df = 1, 38) and a $p = 0.009$ (F = 7.5, df = 1, 38, corrected according to Greenhouse-Geisser) for interaction.

Adverse events

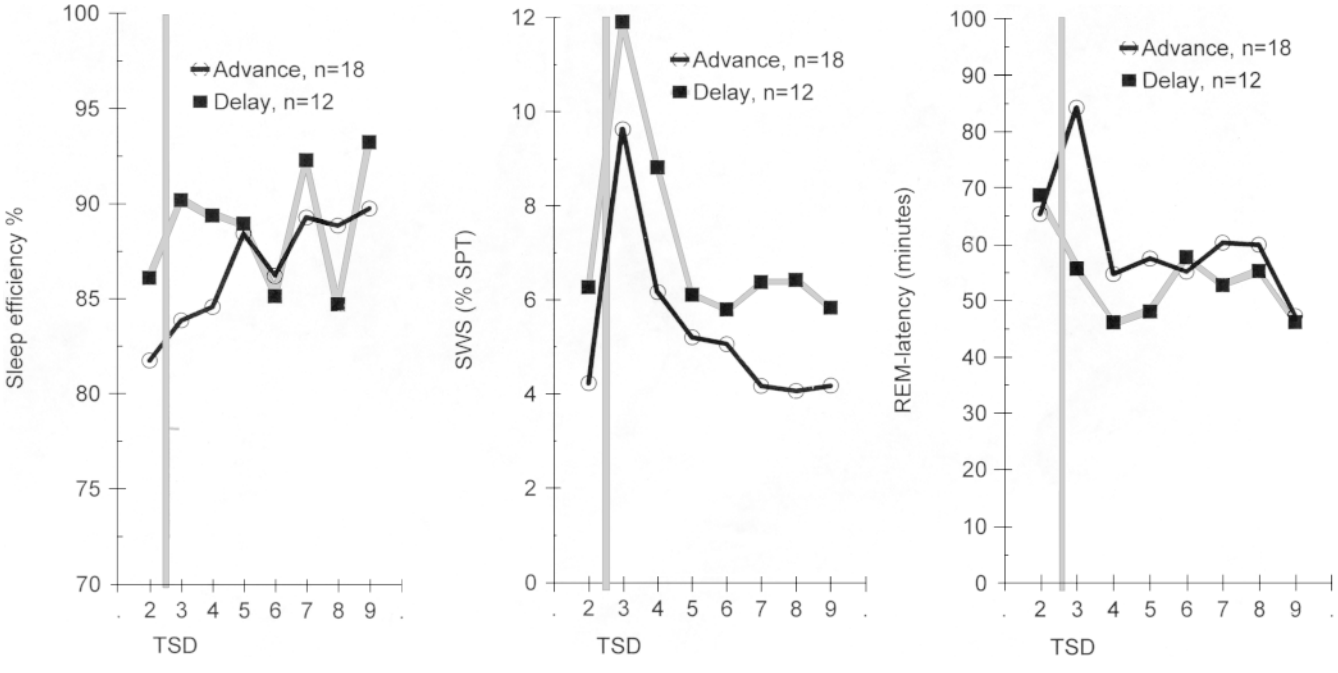
None of the patients showed any serious adverse event during the study period, like the occurence of psychotic or suicidal symptomatology or a switch into mania. Many patients, especially those who relapsed into depression during the study, complained about tiredness, also if their sleep time measured by sleep EEG was not reduced below baseline levels. Between the end of the study and discharge from inpatient treatment one patient had a suicidal crisis 33 days after finishing the study protocol. The symptomatology occured during a weekend stay at home under a continous pharmacological treatment with fluvoxamine, trimipramine, and carbamazepine since one month. This short lasting crisis in this symptomatically improved patient apparently was unrelated to the study.

Polysomnographic data

Mean values (± SD) for the target variables sleep efficiency, SWS %SPT, and REM latency are depicted in Fig. 2.

For statistical analysis an ANOVA with the factors of group (SPA vs. SPD) and repeated measurement (8 nights) was applied. Due to “drop outs” (see above) and additional data losses (due to technical problems – one night

Fig. 2 Mean values (SD) for sleep efficiency, SWS %SPT, and REM latency



each in both experimental conditions) 18 full data sets in the SPA condition and 12 datasets from the SPD condition were used for this analysis.

For sleep efficiency no difference between groups was found ($p = 0.409$, $F = 0.7$, $df = 1, 28$), but a significant effect of repeated measurement ($p = 0.042$, $F = 2.2$, $df = 7, 196$). No significant interaction ($p = 0.437$, $F = 1.0$, $df = 7, 196$) was noted.

SWS % SPT did not differ between groups ($p = 0.545$, $F = 0.4$, $df = 1, 28$), but changed significantly during the study ($p < 0.001$, $F = 11.1$, $df = 7, 196$). No significant interaction occurred ($p = 0.931$, $F = 0.4$, $df = 7, 196$).

REM % SPT (data not shown) also did not differ between the groups ($p = 0.545$, $F = 0.4$, $df = 1, 28$), but displayed significant variation over repeated measurements ($p < 0.001$, $F = 11.1$, $df = 7, 196$). There was no significant interaction ($p = 0.931$, $F = 0.4$, $df = 7, 196$).

In both conditions REM latency was not decisively altered during the study protocol and remained low in a considerable proportion of subjects despite clinical improvement.

The ANOVA did not show a significant group effect ($p = 0.545$, $F = 0.4$, $df = 1, 28$), no change over time ($p = 0.204$, $F = 1.4$, $df = 7, 196$) and no significant interaction ($p = 0.774$, $F = 0.6$, $df = 7, 196$).

With respect to additional hypnotic medication, four patients in both groups required at least one dose of 7.5 mg zopiclone during phase shifting.

Discussion

Analyzing the 6-HAMD data gathered during the study from different viewpoints, either with a dichotomous criterion of 30 or 50% response or analyzing the longitudinal data, confirmed a statistically significant superior effect of SPA compared to SPD on mood. This was also reflected by the full 21-HAMD scale which showed an almost 60% decrease of depressive mood at the end of the study in the SPA group whereas in the SPD group the respective value was 33.5%. In a meta-analysis on the efficacy of TSD [29] it was noted that 83% of unmedicated patients who responded to TSD relapse after the next night of sleep scheduled at a usual bedtime, i.e., only 17% of the patients retained the beneficial effect of TSD after one night of sleep. Insofar the positive effects for a period of 7 days especially in the SPA group clearly argue for the therapeutic value of this sleep-wake manipulation.

Before concluding that SPA is unequivocally a superior treatment compared to SPD, possible pitfalls and caveats need to be discussed.

Though adequate matching of both experimental groups was achieved for age and severity of depression, overall response to TSD was somewhat (statistically significant) weaker for SPD compared to SPA. Nevertheless, all of the patients fullfilled our initial criterion for matching, i.e., at least 30% decrease of the 6-HAMD following TSD. It may be argued that the weaker TSD response precluded subjects in the SPD group from further improvement and led to their high drop-out rate. Homogenization of both groups by applying a stricter 50% response criterion for TSD and phase shifting or by exactly matching both groups according to TSD response still confirmed significantly different treatment outcomes between the two groups, thus, rendering the hypothesis unlikely that the weaker TSD response of SPD patients destinated their poorer outcome at the end of the study. The use of LOCF to analyze our longitudinal data might also be considered as a factor responsible for overestimating therapeutic effects in the group with lower drop-out rates. However, at present we are not aware of a better suited method to deal with the problem of different drop-out rates for a repeated measures design in a therapy study.

Another explanation for the differences found between SPA and SPD might be different or biased expectations of patients concerning treatment efficacy. However, prior to the study no clues were given of the experimenters' hypothesis that SPA is superior to SPD. Insofar we assume that subject expectancy was minimized. At least for TSD alone it has been shown that expectancies towards this treatment are not correlated with treatment outcome [9].

Forty percent of the patients in the SPD condition, who slept during the assumed "depressiogenic" time period, displayed a stabilization of mood during the course of the study. It is hypothesized that this proportion of positive responses in the SPD group may be at least partly due to a placebo effect. It is known from pharmacological trials that a placebo response rate of up to 30 to 40% may occur in uncomplicated depression [20]. In order to accurately estimate the amount of placebo response involved it would be necessary to add another treatment arm, i.e., sleep at usual bedtimes, which we intend to do in future studies.

Polysomnography was performed to test the hypotheses that SPA, due to its use of unusual bedtimes, might lead to a consecutive partial sleep deprivation, thus explaining its therapeutic effect. Concerning sleep efficiency, immediately after TSD, patients in the SPD condition showed higher mean values than the SPA patients. This can be explained from data on sleep physiology and the so-called "2 Process Model" of sleep [7, 8]. At the end of the study, values of both groups were similar. In the SPA group values of sleep efficiency at no time were lower compared to pre-TSD values, thus refuting the assumption of prolonged consecutive sleep deprivation during SPA as an ingredient of this procedure. It might be argued from a different viewpoint (see also 3) that on the other hand the more marked improvement of sleep efficiency in the SPD group – at least during the initial nights after TSD – might be indicative of a sleep related depressiogenic process.

A second purpose of using polysomnography had been to test hypotheses which relate changes in slow wave sleep and REM sleep variables to therapeutic responses [3, 4]. No such correlations were observed in the present study. The reduction in REM sleep immediately after TSD is expected and has been described previously [7]. Usually, SWS is preferentially recovered first, followed on subsequent nights by REM recovery [7]. Surprisingly, the

incidence of very short REM latencies persisted, even in responders to the therapeutic regimens. These data bring into question theories relating sleep, especially REM sleep variables, to the pathophysiology and therapy of depression [see 3, 4]. However, before clear conclusions can be drawn, it will be necessary to investigate healthy controls with our design, in order to evaluate if the sleep-wake manipulations applied have a potency to induce a forward shift of REM sleep, independent of psychopathology.

Summarizing, together with our pilot studies [5, 23] and a recent independent replication [1] the present study suggests that TSD with SPA is an effective and specific chronobiological treatment. From a clinical point of view, TSD with SPA should be considered as an adjunct therapeutic strategy to conventional treatments in order to shorten the considerable time-lag, normally observed between the initiation of antidepressant therapy and significant amelioration of depressed mood. Interestingly, comparably encouraging data have been reported for a combination of sleep deprivation with paroxetine in a sample of 13 patients with geriatric depression [10]. Within this context a recent review article [13] challenges the notion that there is a distinct lag of onset of action with antidepressants. It would be worthwile to apply the suggested strategies to analyze the onset of action of antidepressant drugs also to our treatment approach alone or in combination with psychopharmacological treatment.

Our current investigation gives no answer, whether successful SPA alone has a long lasting effect in depressives, as all of the patients after completing the study, whether responding or not, were switched to antidepressant medication and/or mood stabilizers like lithium or carbamazepin, in most cases in combination with psychotherapy. From an ethical and clinical point of view it was considered necessary to proceed this way to avoid relapses.

Coming to the question of the mechanisms which underlie the therapeutic response to TSD and PA, first of all the hypothesis of REM sleep suppression [see 4] as an important factor in all antidepressant treatments was not confirmed by our data. Other sleep related hypotheses which ascribe either an antidepressant or a depressiogenic property to NonREM sleep or slow wave sleep [see 3], too, are not supported by our observations.

At present the assumption that the avoidance of sleep during a critical time zone, the so-called “internal coincidence model” [25, 26] may be decisive for the therapeutic properties of TSD with SPA seems to be most parsimonious explanation for our results, as this hypothesis is supported by data from nap studies [28], studies with phase advance [18, 19, 22, 26] alone, and results from partial sleep deprivation studies [12, 17]. As sleep or one of its components per se cannot be held solely responsible for antidepressant/depressiogenic properties, the timing of sleep and possibly its interaction with other biological variables might be of utmost importance. In this context, a study in healthy humans [6] using a “forced desynchrony protocol” is of high interest. It was concluded from this study that at least in healthy young subjects, subjectively experienced mood is influenced by a complex and non-additive interaction of the circadian phase and the duration of prior wakefulness. Presently, it is probably too early to generalize findings from this study to sleep-wake rhythms and mood regulation in depression, but hopefully future studies in this direction will further disentangle these complex and fascinating relationships in affective disorders.

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