Sleep Deprivation Combined With Consecutive Sleep Phase Advance as a Fast-Acting Therapy in Depression: An Open Pilot Trial in Medicated and Unmedicated Patients

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Objective: *The authors' goal was to test the hypothesis that the antidepressant effect of total sleep deprivation can be maintained by initially avoiding sleep during a supposedly "critical" time period in the early morning.* *Method:* *They studied 33 inpatients with major depression, melancholic type, all of whom responded positively to total sleep deprivation. Twelve of the patients were men and 21 were women; their mean age was 46.7 years (SD=13.7). After total sleep deprivation, the patients started a sleep schedule from 5:00 p.m. to 12:00 midnight, which then was shifted back by 1 hour each day until a sleep time of 11:00 p.m. to 6:00 a.m. was reached.* *Results:* *Twenty (61%) of the 33 patients who responded to total sleep deprivation with an improved state of mood maintained this improvement during sleep phase advance therapy. Drug-free and medicated patients did not differ from each other.* *Conclusions:* *The rapid amelioration of mood observed with total sleep deprivation can be preserved with a succeeding phase shift of the sleep period.*

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Total sleep deprivation significantly improves mood in about 60% of all depressed patients. The following night of sleep, however, almost regularly leads to a relapse into depression (1). Even short daytime naps can provoke a mood setback. The "depressiogenic" effect of short sleep periods depends on time of day: morning naps have a stronger tendency to provoke relapses than naps in the afternoon (2). In this context, it is of interest that studies involving a total of 20 patients demonstrated that merely advancing the phase of the sleep period to 5:00 p.m. to 12:00 midnight for 2–3 weeks led to an improvement of depression in 75% of the patients (3, 4).

These observations suggest that the "depressiogenic" potential of sleep seems to be restricted to the second half of the night. Therefore, we developed a therapeutic strategy combining total sleep deprivation with consecutive sleep phase advance therapy for 1 week to prevent the usually observed relapse into depression. This procedure initially prevents sleep during the supposedly "critical" time period of the second half of the night (3) and readjusts the sleep schedule in a stepwise fashion.

In continuation of our pilot study (5), which yielded promising results in a small group of depressed patients, we studied a new, independent group of 33 depressed patients (all of whom responded to total sleep deprivation). We treated these patients with a combination of total sleep deprivation and sleep phase advance therapy with the aims of 1) replicating the potency of sleep phase advance therapy to maintain improvement after total sleep deprivation and 2) evaluating whether the antidepressant effect of this procedure is independent of adjunct pharmacotherapy.

METHOD

Thirty-three inpatients (12 men and 21 women) diagnosed according to DSM-III-R as having major depression, melancholic type (unipolar, N=22; bipolar, N=11), participated in the study. Diagnoses were made by using the Structured Clinical Interview for DSM-III-R. The patients' mean age was 46.7 years (SD=13.7). Their mean depression rating on the 21-item Hamilton Depression Rating Scale before they participated in the study was 28.9 (SD=6.5). Sixteen of the patients had been medication free for more than 1 week before participating in the study; these patients remained medication free throughout the protocol. The rest of the patients had been receiving therapeutic doses of antidepressant medication for at least 4 weeks without any notable antidepressant response. In most cases, medicated patients were nonresponders to a stable regimen of 150 mg/day of amitriptyline, which was continued during the study.

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The study was approved by the local ethics committee. After we had provided a complete description of the study to the patients, all of them gave informed written consent before participating.

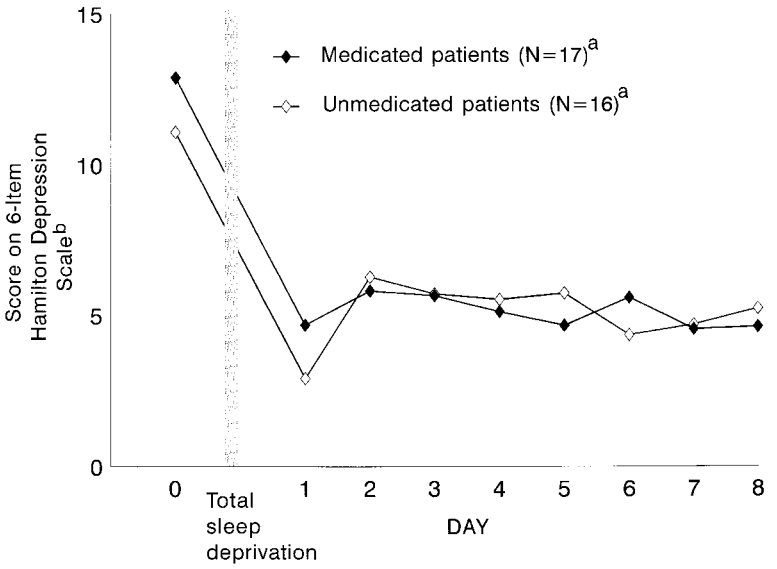
The design in this study followed that of our pilot investigation (5). Two baseline days were followed by total sleep deprivation. For patients who responded to total sleep deprivation (N=33), phase advance of the sleep period started immediately after total sleep deprivation. The sleep schedule for these patients started as 5:00 p.m. to 12:00 midnight. Bedtime was then delayed by 1 hour each day until the conventional bedtime of 11:00 p.m. to 6:00 a.m. was reached after 1 week.

Response to total sleep deprivation was defined as a reduction of at least 30% in the averaged morning (9:00 a.m.) and afternoon (4:00 p.m.) values of a 6-item version of the Hamilton depression scale (6). This response criterion was based on findings from our previous investigations (2). Throughout the study, observer ratings of mood were performed with the 6-item version of the Hamilton depression scale. The ratings were performed twice daily (at 9:00 a.m. and at 4:00 p.m.) by experienced raters who focused on the patient's actual mood state.

Patients were considered responders to sleep phase advance therapy if their mood state (as measured by the 6-item Hamilton depression scale) remained on the level reached immediately after total sleep deprivation, i.e., a reduction of at least 30% in the values before total sleep deprivation.

Using descriptive statistics, we calculated means and standard deviations. For inferential statistics, parametric methods like analysis of variance (ANOVA) or t tests were used; the test of significance was two-tailed. To account for the problem of patients dropping out of treatment before termination of the study (especially in the group of patients who did not respond to sleep phase advance therapy), an endpoint analysis was performed based on the 6-item Hamilton depression scale score achieved before total sleep deprivation, the score achieved directly after total sleep deprivation, and the last score obtained during the study.

FIGURE 1. Impact of Total Sleep Deprivation and Consecutive Sleep Phase Advance on Depressed Mood in 33 Inpatients



[a]Number of subjects varied.
[b]Average of morning (9:00 a.m.) and afternoon (4:00 p.m.) ratings.

RESULTS

Twenty (61%) of the 33 patients who responded positively to total sleep deprivation maintained their improvement of mood during sleep phase advance therapy and finished the study. Thirteen patients (39%) did not respond to sleep phase advance therapy, and seven of these patients dropped out of therapy before the end of the study. When we applied the criterion of a 50% improvement in 21-item Hamilton depression scale scores, we found that 17 (52%) of 33 patients who responded to total sleep deprivation also responded to sleep phase advance therapy.

Mean 6-item Hamilton depression scale values for the 33 patients were 12.0 (SD=3.8) before total sleep deprivation, 3.8 (SD=2.5) immediately after total sleep deprivation, and 7.1 (SD=5.2) at the end of the study. When we compared the different measurements points, we found that mood was significantly improved following total sleep deprivation ($t=12.6$, $df=32$, $p<0.001$) and at the end of the study ($t=6.4$, $df=32$, $p<0.001$). Mean 21-item Hamilton depression scale scores were significantly lower at the end of the study (mean=17.0, SD=10.4) than they were before total sleep deprivation (mean=28.9, SD=6.5) ($t=7.1$, $df=32$, $p<0.001$).

Six-item Hamilton depression scale values for medicated and unmedicated patients during the course of the study are shown in figure 1.

The 6-item Hamilton depression scale values did not differ in medicated and unmedicated patients over the course of the study (for medication status, $F=1.0$, $df=1, 31$, $p=0.32$; for repeated measurements, $F=52.0$, $df=2, 62$, $p<0.001$; and for their interaction, $F=1.3$, $df=2, 62$, $p=0.29$, two-factor ANOVA). The dropout rate was comparable in both groups as well: four of 17 medicated and three of 16 unmedicated patients did not finish the study because of nonresponse.

DISCUSSION

Twenty (61%) of 33 depressed patients who responded positively to sleep deprivation maintained their improved mood level during a sleep phase advance protocol. Even with the stricter criterion for improvement—a 50% reduction in 21-item Hamilton depression scale scores—a substantial number of patients (N=17; 52%) qualified as responders to sleep phase advance therapy. This change in psychopathology occurred immediately—during one night of sleep deprivation—and was sustained. In contrast, only 20% of patients who responded to total sleep deprivation did not relapse when they resumed a normal sleep schedule following total sleep deprivation (1). Data from other studies (3, 4) demonstrate that even without a preceding successful total sleep deprivation, sleep phase ad-

vance therapy for 2–3 weeks alleviated depressive mood in 75% of patients. However, total sleep deprivation guarantees a swift improvement of mood and facilitates the participation in the following procedure. Additionally, it limits sleep phase advance therapy to 1 week, with a gradual return to the conventional sleep schedule, which is easier and more tolerable for patients.

The existing studies on sleep phase advance therapy with or without a preceding total sleep deprivation cannot exclude the possibility that part of the 60% response found in this study may be a placebo effect. A double-blind comparison of the suggested strategy with another therapeutic regimen is not possible, however.

Patients treated simultaneously with antidepressants did not show a stronger response to the procedure than unmedicated patients, thus refuting the assumption that the effects observed in our pilot study (5) were due to a synergistic effect of medication and sleep phase advance.

The findings of the present study demonstrate that it is possible to enhance the clinical effect of total sleep deprivation by combining it with succeeding sleep phase advance therapy. Compared with established antidepressive strategies like pharmacotherapy, ECT, or psychotherapy, which take at least 2 or 3 weeks to have a a clinically relevant effect, this procedure seems to offer the chance to shorten the time lag between the initiation of therapy and the onset of significant improvement.

REFERENCES

1. Wu JC, Bunney WE: The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. Am J Psychiatry 1990; 147:14–21
2. Wiegand M, Riemann D, Schreiber W, Lauer ChJ, Berger M: Effect of morning and afternoon naps on mood after total sleep deprivation in patients with major depression. Biol Psychiatry 1993; 33:467–476
3. Wehr TA, Wirz-Justice A, Goodwin FK, Duncan W, Gillin JC: Phase advance of the circadian sleep-wake cycle as an antidepressant. Science 1979; 206:710–713
4. Souêtre E, Salvati E, Candito M, Darcourt G: Biological clocks in depression: phaseshift experiments revisited. Eur Psychiatry 1991; 6:21–29
5. Vollmann J, Berger M: Sleep deprivation with consecutive sleep phase advance therapy in patients with major depression: a pilot study. Biol Psychiatry 1993; 33:54–57
6. Bech P, Gram LF, Dein E, Jacobson O, Vitger J, Bohnys TG: Quantitative ratings of depressive states. Acta Psychiatr Scand 1975; 51:161–170