Sleep deprivation and antidepressant treatment

The mood-improving effect of sleep deprivation (SD) in depression is even today still not fully understood. Despite the fact that mood and cognitive functions are lowered by prolonged sleep loss and despite convincing data that insomnia is a strong risk factor for subsequent depression,[1] acute SD for one night or even partial SD in the second half of the night improves mood in about 60% of depressed patients the day after.[2,3] In this respect, among all types of antidepressant treatments, SD elicits the fastest results, faster even than electroconvulsive therapy. Many authors correlate the likelihood of responding to SD with clinical variables. A summary of predictors is listed in Table I.

The main limitation is the transient nature of the effect, since the majority—but not all—of the improved patients experience a relapse after the next night of sleep.[2]
Despite the rapid effects and low risk of relevant side effects *(Table I)*,[2-9] the method has remained an "orphan drug" or "orphan method." This may be explained not only by the effort and motivation needed by the patient and by the frequent relapses after the next night of sleep, but also by the lack of funding for nonpharmacological and nonneurochemical research. Nevertheless, some progress has been made within the last few years. A variety of studies have focused on the problem of how to avoid relapses occurring after the next night of sleep and additionally treated the patients with light therapy, lithium, or other drugs. Lower relapse rates after SD were found when SD was combined with one of these therapeutic options *(Table II)*.[10-20]
A further strategy has been to advance the sleep period to an "unphysiological" time. Several uncontrolled studies in small numbers of patients have indicated that this phase advance procedure per se acts as an antidepressant. More recent studies have combined SD with a subsequent phase advance of the sleep period, over the course of either six or three nights and consistently found that a phase advance of the sleep period stabilizes the antidepressant effect of SD in about 60% of those patients who responded positively to SD.[17-20] Only one study also included a control group which participated in a phase-delay protocol after SD instead of a phase-advance protocol.[18] Significantly more patients relapsed in the phase-delay protocol compared with the phase advance protocol *(Figure 1)*. This indicates that the high

Predictive
- High level of arousal[4]
- High variability of mood swings[5]
- Diurnal and day-to-day mood variations[6]
- "Endogenous" and melancholic subtype[2,3]
- Bipolar subtype[7]

Not predictive[2,3]
- Age
- Sex
- Severity of depression
- Duration of depressive episode
- Duration of illness
- Earlier treatments
- Expectation of patients

Side effects of SD in depression*
- Tiredness, fatigue
- Switch to hypomania or mania in bipolar patients[8]
- Exacerbation of psychotic symptoms in psychotically depressed patients[9]
- Lowering of seizure threshold

Table I. Clinical predictors of an antidepressant response to sleep deprivation (SD) in depressed subjects and side effects. *Not based on systematic documentation.

- Antidepressants (clomipramine)[10]
- Lithium[11-13]
- Pindolol[14]
- Light therapy[15,16]
- Sleep phase advance over 3 to 6 nights[17-20]

Table II. Therapeutic strategies to avoid relapses after successful sleep deprivation in depression (selected papers).

Poster by: Ulrich Voderholzer, MD, PhD
Department of Psychiatry and Psychotherapy,
Klinikum of the Albert-Ludwig-University,
Hauptstrasse 5, 79104 Freiburg, Germany
(Ulrich_Voderholzer@psyallg.ukl.uni-freiburg.de)

response rate after SD and phase advance cannot be explained by a placebo phenomenon alone and supports the hypothesis that, in depressed subjects, sleeping at certain phases of the circadian rhythm, ie, especially late in the night and in the morning, has depressogenic effects.
Unfortunately, one major issue has been almost completely neglected by researchers: does SD produce any lasting effects after 4 to 6 weeks, which is the typical period for measuring the effects of antidepressants? There is only one controlled study using such a design.[21] Twenty-four patients received amitriptyline without additional SD, whereas 27 patients received amitriptyline plus a series of 6 partial SDs. Observer ratings, but not patient ratings, demonstrated superiority of the combined treatment after 4 weeks. By the standards of evidence-based medicine, there is little evidence to date that SD therapy has lasting effects over the course of several weeks.

Neurobiology of SD in depression

There is no generally accepted hypothesis concerning the mechanism of action of SD, nor an explanation for the observation that subsequent sleep after SD leads to relapses. A variety of neurobiological effects point toward potential mechanisms of action of the procedure *(Table III)*.[22-32]
Based on the observations that hyperarousal and a high level of activation predict a favorable SD response,[4] the antidepressant effect was explained using the two-process model of sleep regulation *(Figure 2)*.[33] In this model, depressed patients have a deficiency of process S (ie, sleep need) with process C (circadian rhythm) remaining unaffected. Depression is characterized by a deficient build-up of process S *(Figure 2)*. SD transiently leads to an increase in process S to normal, whereas relapse occurs after "recovery sleep" due to a return to low levels of S.
Several brain imaging studies have tried to correlate the SD response with metabolic states of certain brain areas. Two early studies using single photon emission computed tomography (SPECT)[22] and positron emission tomography (PET),[23] respectively, found higher metabolic rates in limbic areas in responders compared with nonresponders. A more recent study[24] confirmed these earlier findings: responders to SD had higher relative metabolic rates in the ventral anterior cingulate and in the medial prefrontal cortex *(Figure 3)*, as well as in the posterior subcallosal gyrus at baseline than depressed patients who did not respond to SD and normal volunteers. After SD,

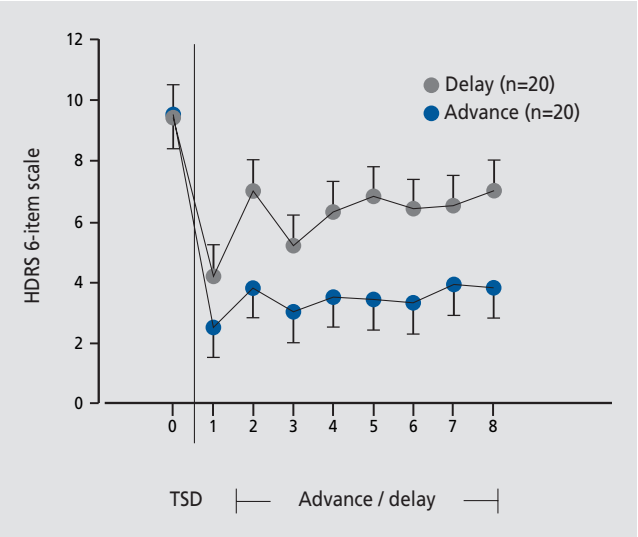
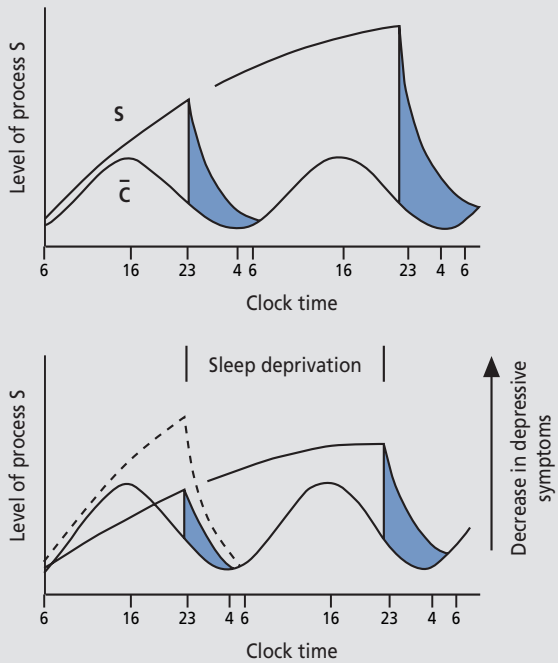


Figure 1. Antidepressant effects of total sleep deprivation (TSD) in one night with a consecutive phase advance of the sleep period (blue circles) in comparison with a phase delay of the sleep period (gray circles). In the phase-advance group, the antidepressant effect of SD (between day 0 and day 1) was stabilized until day 8, whereas in the phase-delay group mood worsened again (mood was measured by a short version of the Hamilton Depression Rating Scale [HDRS], containing 6 items). This scale is suitable for frequent ratings, whereas the 21-item HDRS would not have been adequate within the study design.[18]

- Decrease in limbic hypermetabolism[22-24]
- Increase in dopamine turnover[25]
- Increase in peripheral cytokines[26,27]
- Increase in cortisol[28-30]
- Increase in growth hormone secretion (recovery sleep)[30]
- Increase in thyroid hormones[31,32]

Table III. Neurobiological effects of sleep deprivation. In humans some of the studies were performed in depressed patients, while other studies were in healthy subjects or in depressed patients and healthy subjects.

significant decreases in metabolic rates occurred in the medial prefrontal cortex and frontal pole in the patients who responded positively to SD. The brain imaging studies convincingly demonstrated that acute antidepressant SD is able to change metabolic states of brain areas that are involved in mood regulation.
Many studies have assessed endocrine parameters before and after SD. The results have been inconsistent, which may be partially explained by methodological shortcomings. Several authors favor the hypothesis that the hypothalamo-pituitary-thyroid (HPT) axis plays a key role in mediating the antidepressant effects of SD.[31,32]



Another issue is the impact of SD on the hypothalamo-pituitary-adrenal (HPA) axis. Increased activity of this axis is one of the most consistent abnormalities in depression and normalization of this hyperactivity is a correlate of clinical remission and has been suggested as the mechanism of action of antidepressant treatment.[34] In healthy humans, acute SD increases cortisol secretion.[28,29] In a study that we conducted ourselves, we found a significant stimulatory effect of acute SD on nighttime cortisol in a group of unmedicated depressed subjects, which was not related to treatment response.[30] However, during the first

Figure 2. Two-process model of sleep deprivation (SD) and depression . This model can explain the antidepressant effect of SD by assuming that an insufficient build-up of process S (S stands for sleep need), SD transiently increases the level of process S, thus, leading to the antidepressant effect. Recovery sleep decreases process S to baseline levels leading to relapse into the depressed state. This model fits well with clinical observations that depressed patients have hyperarousal, which has been shown to be a positive predictor of the SD response.[4]
Reproduced from reference 33: Borbély AA, Wirz-Justice A. Sleep, sleep deprivation and depression. *Hum Neurobiol*. 1982;1:205-210. Copyright © 1982, Springer Verlag.

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half of the day after the night, SD responders in contrast to nonresponders had higher cortisol concentrations compared with the day before SD. This finding does not necessarily contradict the above relationship between depression and HPA axis hyperactivity for two reasons. First, the acute effects of antidepressant treatments on the HPA axis may differ from the chronic effects. It has been shown that electroconvulsive treatment and antidepressants also initially stimulate the HPA axis. Second, two studies demonstrated acute antidepressant effects of cortisol infusion compared with placebo.[35,36]

Another theory that possibly provides a link to the HPA effects of SD focuses on the psychostimulant effects. Earlier studies reported an increase in dopamine, norepinephrine, and serotonin after SD, ie, similar neurobiological effects as after the intake of psychostimulants like amphetamines (see reference 25 for an overview). Support for a psycho-stimulant theory also comes from brain imaging data, demonstrating effects of psychostimulants such as amphetamines on metabolic rates similar to those observed in SD.[37] Since there is a functional coupling of psychostimulant effects and the HPA axis,[38] a cortisol increase following SD might therefore mediate psychostimulant-like actions of increased aminergic neurotransmitter release.

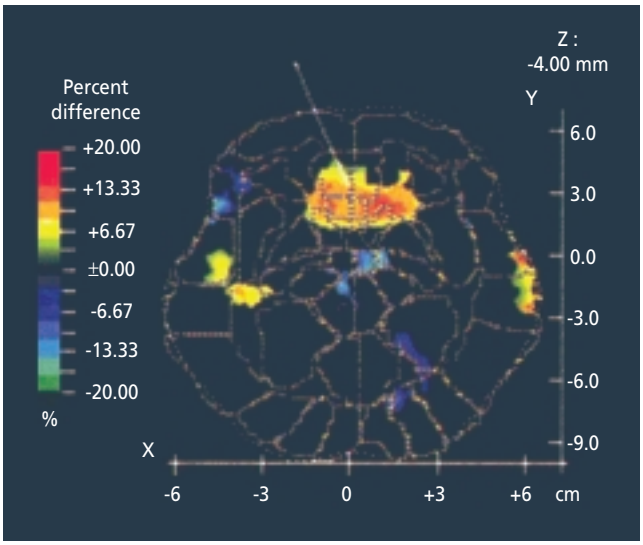

Figure 3. Positron emission tomography (PET) scan of depressed patients who respond to total sleep deprivation (SD) in one night.[24] At baseline, responders to SD had higher metabolic rates in the ventral anterior cingulate and in the medial prefrontal cortex. The study confirmed earlier findings demonstrating an association between high metabolic rates in limbic areas and the likelihood to respond to SD.[22,23]
Adapted from reference 24: Wu J, Buchsbaum MS, Gillin JC, et al. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *Am J Psychiatry*. 1999;156:1149-1158. Copyright © 1999, American Psychiatry Association.

In summary, the SD response in depressive patients remains a highly interesting issue for depression research, since, contrary to all antidepressant drugs, it may significantly ameliorate mood within one day. Understanding this effect and optimizing the duration of the effect, ie, preventing relapse after the response, might improve our ability to treat depression.

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