EXPERT REVIEWS

Sleep deprivation in depression

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Sleep deprivation (SD) is a powerful antidepressant treatment that shows antidepressant responses within hours in 40–60% of depressed patients. In more than 80% of responders to SD, a relapse into depression occurred after the recovery night. In addition, it serves as an excellent tool to examine the neurobiological disturbance of depression and may profoundly contribute to the development of new specific and more rapidly acting antidepressants. The reason why SD works and relapses occur is still unclear. A key to solve this problem is to include the current knowledge about the neurobiological disturbance of depression in research, with a focus on neurobiological aspects of sleep and SD (sleep EEG, neuroendocrinology, neurochemistry and chronobiology). Based on findings from these different areas, different strategies to stabilize the antidepressant effect of SD have been applied. This article provides an overview of clinical and neurobiological responses related to SD in depression.

Keywords: depression • dopamine • GABA • microsleep • naps • neuroimaging • serotonin • sleep deprivation • sleep EEG • sleep endocrinoloy • sleep regulation

Sleep deprivation (SD) as a nonpharmacological antidepressant therapy was introduced approximately 40 years ago. Case observations by Schulte [1] and Pflug and Tölle [2] were the first to provide evidence of the antidepressant effect of SD, which is also called 'induced-wakefullness therapy', for 1 night in depressed patients. Since then, clinical and theoretical interest in therapeutic SD has increased worldwide. SD has proved to be an easily applied form of antidepressant treatment. However, in almost all patients the effect is not stable. Owing to the acute response to SD, this method lends itself as a model for research into the basic neurobiological mechanisms underlying depression and antidepressant treatment.

In the 1990s in particular, many psychiatrists were convinced of the extraordinary importance of this phenomenon, and a number of articles have been addressing the issue of therapeutic SD concerning prediction of response and stabilization of the transient effect.

In recent years, the original interest in clinical research and application has decreased. Publications on the topic of SD focused more on the underlying neurobiological mechanisms, which to date are more clear, but still unsolved.

Owing to the rapidity of change in mood, it is unlikely that psychological mechanisms can provide a complete explanation. Focus on the neurobiology of depression and the invention and integration of new methods in psychiatric research, such as neuroradiology and neuroendocrinology, have evolved a number of new findings on brain function in depression, which also touch on the relationship between SD and depression.

Therefore, this article will not update previous summaries (e.g., [3–6]), but instead the objective is to integrate neurobiological data on depression and SD research into the current knowledge of clinical effects and therapeutic application of SD.

Clinical effects of SD

Based on the early case reports and the study of Pflug and Tölle [2], the main feature of SD compared with all other antidepressant treatment strategies is the short-term response that happens within hours during the extended wakefulness, already starting during the SD night. More than two-thirds of patients present with a moderate-to-marked response of 20–60% improvement compared with baseline values [7,8]. In a meta-analysis of 61 studies, Wu and Bunney report on a marked antidepressive effect in 59% of the patients [3]. Based on these data, it is obvious that approximately a third of patients do not benefit from SD. These patients usually do not alter in psychopathology, and the only effect of SD observed in these nonresponding patients is an increase in tiredness [4]. Very rarely, SD may intensify depressive symptomatology. In these patients, agitation and restlessness associated with exhaustion may become predominant

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during SD [4,9]. A total of 10–15% of sleep-deprived patients respond after the recovery night only; they are called day 2 responders [8].

The side effects of SD that have been described include vegetative symptoms and fatigue [10], and also headache in some cases [11]. The only contraindication is epilepsy, as SD has a high risk of inducing seizures in patients with this condition [12]. In addition, nonspecific stress associated with staying awake all night could lead to unexpected medical conditions in a very low number of patients with somatic illness [13,14].

Several studies report that symptoms that are favorably influenced by SD are suicidal tendencies and psychomotor inhibition [2,15]. Pflug reported more favorable responses in depressive mood than on psychomotor disturbances [10]. The report of Kraft *et al.* demonstrated that SD also exerts a favorable effect on thought content (i.e., affecting negative cognitions of depressed patients) [16], and is underlined by the finding that responses to positively loaded associations of an emotional Stroop paradigm will increase, and to negatively loaded associations decrease, during SD in SD responders [17].

Men and women respond equally well. Neither age, number of hospitalizations, earlier treatments, duration of episode or severity of depression appear consistently related to responsiveness to SD [4,6].

Positive responses to SD have also been reported for patients with depressive syndromes based on diagnoses other than unipolar depression, such as patients with schizophrenia and negative symptoms and post-schizophrenic depression, patients with premenstrual syndrome and, in particular, patients with bipolar depression [6,18]. The latter group of patients may even respond better than recurrent unipolar depressed patients [19]. However, approximately 25% of bipolar patients may switch to mania or hypomania during SD. This response is mainly characteristic for bipolar patients with rapid cycling, as bipolar patients without rapid cycling present with a lower switch rate of approximately 5% [17]. Lithium or other prophylactic medication can reduce this switch rate [20].

Sleep loss can be a trigger for the development of manic symptoms in bipolar disorder, as night-time sleep duration is negatively correlated with manic syndromes [21]. The fact that bipolar patients may react to SD with an exaggerated mood elevation, and that sleep loss induces manic symptoms in these patients, points to the close relationship between sleep/wake regulation and modulation of mood, which is a fundamental observation for an approach to the scientific research on this topic.

Relationship between recovery night sleep, naps, microsleep & relapse

The great advantage of SD is the short-term, sometimes immediate, response compared with other antidepressant treatment strategies. However, the most striking disadvantage is the relapse into depression in most of the patients after the first night of sleep (recovery night) [3,22].

Wu and Bunney reported in their survey that relapse occurs in approximately 83% of unmedicated responders after the recovery night [3]. Concomitant antidepressant medication may prevent relapses, as only 53% of medicated responders relapsed in this meta-analysis [3].

Impact of naps & microsleep on SD response

The observation that after the recovery night a great majority of SD responders relapse into depression suggests that sleep *per se* may have a depressiogenic property. Furthermore, it is not only sleep of the recovery night, also short naps during 'induced wakefulness' that may lead to an immediate relapse into depression in SD responders. This was first reported as single case observations [22,23]. Roy-Byrne and colleagues described a case of a patient who relapsed even after a very brief nap of some minutes [22].

The detrimental effect of naps on mood has been systematically examined by Wiegand and Berger in several studies [24,25]. They evaluated 85 SD therapies in 50 depressed patients and varied the times (9 am, 1 pm and 3 pm) in which patients should nap during SD.

A total of 21 naps induced a marked relapse after an antidepressant response to SD, 23 naps evoked a mild-to-moderate relapse and 18 naps did not induce any major changes of depressive symptoms. First, the authors could demonstrate that naps generally trigger an immediate relapse in SD responders lasting until the evening of the SD day. A more detailed analysis of these studies showed that naps in the morning hours were significantly more related to a relapse than naps in the afternoon and evening hours of the SD day [26]. From the findings of these studies it is concluded that naps in the morning of the SD day have a higher risk for relapse than naps in the later part of the SD day.

In nonresponders to SD, according to the data of Wiegand *et al.,* naps have no effect on mood [24]. By contrast, Gillin *et al.* reported a favorable effect of naps in nonresponders [27]. This observation, together with the fact that 10–15% of patients show a day 2 response after the recovery night, contradicts the hypothesis that sleep *per se* might be depressiogenic in general.

Polysomnographic recordings of naps demonstrated that relapse into depression occurred irrespective of the presence of rapid eye movement (REM) sleep or non-REM sleep during the naps [28].

Based on data from a study in which sleep EEG has been, for the first time, continuously recorded over 24 h in depressed patients, it has been shown that during waketime repeatedly short and ultrashort episodes of sleepiness and sleep occurred, which were distributed – in contrast to healthy controls – unsystematically across the entire waketime [29].

In a single case report by Southmayd *et al.,* comparable phases of sleepiness by EEG recording could be detected during SD in a depressed patient [30]. These short episodes of sleep had not been recognized by the patient himself or by the nursing staff.

Based on these results, it has been suggested that not only intended naps during SD (see studies of Berger, Riemann and Wiegand [24–26,28]), but also short, even ultrashort, episodes of sleep (microsleep) during SD, may prevent the antidepressant response to partial SD (PSD) or induce a relapse.

These considerations have been addressed in one of our own studies [31], in which depressed patients who underwent a PSD (second half of the night) were monitored continuously over 60 h by EEG recording for the assessment of baseline sleep EEG, a

sleep EEG immediately before PSD and a sleep EEG of the recovery night. In addition, the EEG during the entire waketime before and during SD was recorded in order to assess the amount of microsleep during wakefulness. The results of this study showed that microsleep was already present before SD, and increased in the mean from 11.4 up to 33.4 min in the total group. Dividing patients by a median split, according to the amount of microsleep during SD, into two groups revealed that patients who did not present with a high amount of microsleep during PSD were in a significantly better mood than patients with a high amount of microsleep during PSD (Figure 1). The relationship between microsleep and mood observed in this study could be confirmed by a further study from another group using total SD (TSD) in depressed patients [32]. They also demonstrated that nonresponders presented with an increased amount of microsleep in total, and in particular during the SD night until the 'critical' morning hours.

Sleep EEG & sleep endocrine secretion in depression

In all the aforementioned observations, SD exerts an antidepressive effect and sleep, either in the recovery night or also in terms of very short naps or unaware microsleep episodes during the day of SD, was followed by a relapse into depression, suggesting that sleep is closely related to the variation of mood and may have a depressiogenic effect in at least the majority of patients with depression. Therefore, the detailed evaluation of sleep in depression and under SD conditions may be key for the clarification of underlying mechanisms of the SD phenomenon in depression.

It is well established that in almost all patients with depression, sleep is disturbed (e.g., [33]). On the level of behavior, sleep disturbance in depression is characterized by a prolonged sleep onset latency, difficulties in sleep maintenance and early morning awakening with the inability to return to sleep.

Polysomnographic evaluation of sleep in depressed patients provides more insight into sleep architecture and REM sleep alterations in these patients. Besides the disturbance of sleep continuity with reduced sleep efficiency, sleep in major depression is polysomnographically characterized by a distinct sleep EEG pattern, including reduced non-REM sleep pressure (less slow-wave sleep [SWS] and slow-wave activity [SWA] and typical alterations of REM sleep [i.e., reduced REM latency, increased REM density]) [34,35].

Models of sleep regulation

There are models of sleep regulation that have some heuristic value for the explanation of the characteristic sleep disturbance in depression. In addition, these models may have an additional prognostic value for the reactivity of patients to the SD intervention.

Two-process model of SD & S-deficiency hypothesis

The two-process model of sleep regulation with the two components, process S for the homeostatic and process C for the circadian modulation of sleepiness, provides an explanation for the characteristic sleep EEG pattern in depression [36,37], suggesting a deficiency of the homeostatic component, the process S [37]. Therefore, sleep onset latency is prolonged and sleep pressure reflected by diminished SWS and SWA is reduced, allowing REM sleep to increase and advance, reflected by the characteristic REM sleep abnormalities in depression (shortened REM latency and increased REM sleep and REM density at the beginning of the night).

In healthy subjects, experimentally scheduled naps during normal and extended wakefulness were able to reduce process S [38–40]. The same mechanism may occur in depressed patients who present with microsleep during the day. This suggestion is supported by the finding that a high amount of microsleep during SD is related to less SWS in the recovery night [31].

Therefore, naps and microsleep during SD may weaken the accumulation of process S that may be related to SD nonresponse [26,31,41].

Aminergic–cholinergic interaction model

An alternative explanation for the sleep abnormities in depression is provided by the reciprocal aminergic–cholinergic interaction model [42], which – in addition to the model of Borbely – provides an explanation for the alternate change from non-REM to REM sleep within sleep cycles. As REM sleep is regulated by cholinergic neurotransmission and non-REM sleep by aminergic neurotransmission, this model suggests a relative preponderance of cholinergic to aminergic neurotransmission, which is responsible for the increase and advance of REM sleep within the sleep cycles and the reduction of aminergic-guided non-REM sleep, in particular in the first sleep cycle.

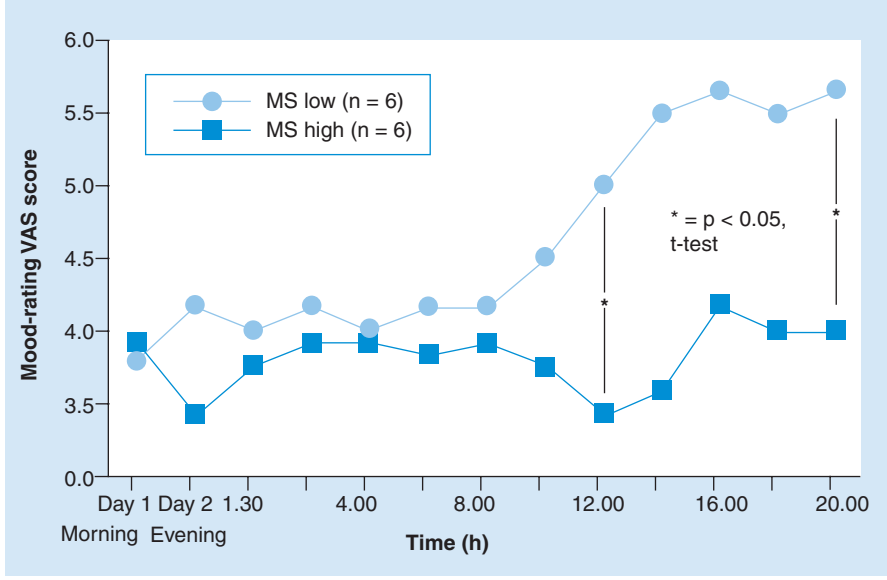

Figure 1. Mood response in patients with a low and a high amount of microsleep during partial sleep deprivation.
MS: Microsleep; VAS: Visual analog scales.

Extended two-process model of sleep regulation

Further evidence for a neurobiological basis of sleep disturbance in depression and a possible relation to SD response comes from sleep endocrine studies in which sleep EEG and hormonal secretion have been measured in parallel.

In major depression, the neuroendocrine disturbance characterized by the hyperactivity and dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis is well established. This is reflected by an increased 24-h cortisol secretion, nonsuppression in the dexamethasone (DEX) suppression test (DST) and exaggerated response in the combined DEX–corticotropin-releasing hormone (CRH) test [43]. All these findings are explained by a hyperactivity of CRH secretion.

During sleep, HPA axis abnormalities can also be observed – that is, an increased cortisol secretion during the night, a reduced latency until the cortisol rise in the second half of the night and an increased nadir of cortisol secretion [44].

In addition, nocturnal growth hormone secretion is also altered in depression, showing a reduced peak at the beginning of the night [45].

Sleep endocrine studies revealed a close link between neuroendocrine disturbance in depression and the depression-like sleep EEG pattern. From experimental studies with animals and healthy subjects, it is known that a pulsatile application of CRH is able to induce a sleep endocrine profile comparable with that of depressed patients with an increased sleep onset, reduced SWS, increase of REM sleep and early morning awakening [46]. The application of growth hormone-releasing hormone (GHRH), at least in healthy males, induced, in part, opposite effects. Besides an increase of the sleep-related growth hormone peak, sleep efficiency was improved and SWS increased [47].

Based on these findings, the extended two-process model of sleep regulation has been suggested, which relates the HPA axis with cortisol secretion as the peripheral parameter to process C (the circadian component in the model of Borbely) and the hypothalamus–pituitary–somatotropic axis to process S, which can be augmented by GHRH injections [44].

In major depression, it is suggested that CRH activity is relatively increased compared with GHRH activity at the beginning of the night. This can explain the sleep endocrine differences between healthy controls and depressed patients, characterized by an increased and advanced cortisol secretion, a reduced CRH peak and the characteristic sleep EEG pattern with increased and advanced REM sleep and reduced non-REM sleep pressure [44,48].

Effects of SD on sleep EEG & nocturnal neuroendocrine secretion

Sleep EEG effects of SD

Sleep deprivation in healthy subjects leads to an improvement of sleep continuity and to an augmentation of non-REM sleep (in particular an increase of SWA or SWS) and, in addition, REM sleep may be slightly intensified in the recovery night [49–51].

In depressed patients, the observed effects were widely similar, but with a larger variation concerning the effects on sleep architecture and REM sleep parameters. Furthermore, a reduction of REM latency has also been observed [31,52,53]. Almost all depressed patients show an improved sleep continuity after SD, even if they do not respond with improved psychopathology [54]. Therefore, SD may be used as an additional treatment, especially in depressed patients with an intense, treatment-resistant insomnia.

The effects of SD on sleep EEG are in line with the two-process model of sleep regulation, as it predicts that prolongation of wakefulness strengthens process S, which is reflected by an increase of SWS and SWA and, consequently, a prolongation of REM latency in the recovery night. In addition, the observed effects on sleep EEG may also be explained by the cholinergic–aminergic interaction model, as SD may intensify the aminergic component (and probably weaken the cholinergic component), which leads to a prolongation of the first non-REM episode and an increase in REM latency, and also a decrease of REM sleep in the first sleep cycle. While there are already a number of data that support the aminergic role in SD (see later), further research, especially human studies, are needed.

Nocturnal endocrine effects of SD

Sleep deprivation also has major effects on hormonal secretion during SD and during the recovery night. During SD, sleep-onset-associated growth hormone secretion is strongly reduced, while in the recovery night it is increased compared with baseline, and related to the observed SWS increase [55,56]. The same pattern is observed for prolactin [57]. Growth hormone secretion is suppressed during SD [57,58] and increased in the recovery night compared with baseline.

Studies investigating the influence of SD on cortisol secretion in healthy subjects revealed conflicting results. No effect on cortisol has been observed in the recovery night [55,59,60]; however, two studies in depressed patients reported a reduction of cortisol [56,61].

According to Vgontzas and coworkers, the reduced cortisol might reflect a reduction in CRH activity, which may be the underlying mechanism of SD effects in depression [56]. However, during SD in depressed patients, cortisol secretion is increased [57,62–65]. This effect was more pronounced in SD responders [57,66].

In one study, cortisol was measured during SD continuously until the end of the recovery night in depressed patients [67]. In this study, cortisol levels during SD were significantly higher than at baseline. Predominantly, SD responders presented with higher cortisol levels in the first half of the day of SD.

There are also studies that evaluated the function of the HPA axis with the DST or the combined DEX suppression CRH-stimulation test (DEX–CRH test) in relation to SD response. DST suppressors showed a better mood response to SD than non-suppressors in two studies [68,69], although there are also different results (e.g., [70]). The DST findings and the previously described cortisol increase during SD in responders [57,67] may reflect the fact that SD responders have a less or undisturbed regulation of the HPA axis than SD nonresponders.

In addition, thyroid-stimulating hormone secretion has been shown to be consistently stimulated by SD [9,57,71]. However, this observation may be secondary to a reduction of the

thyrotropin-releasing hormone by SD, as the thyrotropin-releasing hormone can be regarded as a cofactor to CRH in the extended two-process model of sleep regulation [72].

No relationship to SD response has been observed for thyroid-stimulating hormone and prolactin [57,73]. Murck *et al.* also found a strong increase of renin in the recovery night, suggesting that the rennin–angiotensin–aldosterone system is involved in SD effects [74].

The observed effects on hormonal secretion are also in line with the extended two-process model of sleep regulation, as SD may augment process S and related GHRH secretion, reflected by an increased growth hormone peak and – this has not been so clearly shown – a reduced cortisol secretion in the recovery night based on reduced CRH activity.

There is only one human study that has been performed to test the extended two-process model. The fact that SWA increase after SD was closely correlated to an increase of the growth hormone/cortisol ratio in recovery sleep indirectly supports the assumptions of the extended two-process model during SD [75].

Modes of SD

Besides TSD (deprived sleep in the total night), PSD in the first and the second night and selective REM SD have also been therapeutically applied to depressed patients (**Box 1**) (see [76,77]).

Partial SD (early vs late PSD)

A number of studies have been performed to evaluate the effect of PSD that can be performed as early (first half of the night until 1.30 am) or late PSD (second half of the night from 1.30 am). The introduction of PSD has led to a marked improvement of SD tolerance, as the interval of induced wakefulness becomes much shorter. This represents a considerable relief for the patients.

Several studies show that late PSD is equally as effective as TSD [78]. In addition, late PSD (and TSD) seems to be superior to early PSD [79–81], although there are data showing that SD in the first half of the night may be equally effective as in the second half of the night, if equal sleep duration is provided [8,82]. Taken together, these findings show response to late PSD is more evidence-based than to early PSD. Furthermore, it is assumed that late PSD beginning at 1.30 am is at the turning point on mood – based on the experience with TSD – and the nocturnal minimum of essential psychophysiological parameters (i.e., rectal temperature, heart rate and blood pressure) occur later in the night [7]. Also, a PSD starting at 2.30 am showed a comparable effect on mood to PSD starting at 1.30 am. By contrast, PSD following a waking time of 3.00 am or later was clearly less effective than with an earlier beginning [83].

REM SD

Based on the fact that REM sleep is increased and advanced in the sleep EEG pattern of depressed patients, and based on the observation that most antidepressants suppress REM sleep, it has been suggested that REM sleep reduction is a prerequisite for the achievement of an antidepressant effect. Vogel and colleagues addressed this question by depriving REM sleep through selective awakenings from REM sleep over a period of 3 weeks with endogenously depressed patients [84]. They were able to reduce REM sleep by approximately 50%, and achieved an antidepressant response comparable with a treatment with the tricyclic substance imipramine.

By contrast, the control group, which was selectively deprived of non-REM sleep, did not show any clinical response. In addition, REM SD for only 2 nights did not exert a clinical response [85].

Only one further study addressed the issue of selective REM SD. In addition to the study of Vogel *et al.* [84], selective REM SD was compared with the same amount of well-balanced awakenings leading to non-REM SD in depressed patients [86]. While REM SD in this study exerted an antidepressant effect comparable with the study of Vogel *et al.*, non-REM SD led to an even stronger antidepressant effect. In both conditions (REM and non-REM SD), a prolongation of the duration of non-REM sleep cycles was observed and, therefore, postulated as the common underlying mechanism of action for the antidepressant property of both treatments.

In this context, it has to be noted that REM SD is always accompanied by a gradual suppression of non-REM sleep [50,87]. As REM SD leads to a gradual (and not acute) improvement of mood, it has been suggested that the suppression of SWA in REM SD is also causal to the antidepressant effects of both REM sleep and total SD [88].

However, the application of REM SD under clinical conditions is not realistic as it requires many nights (and man-hours) in the sleep laboratory. Therefore, REM SD may currently be more a matter of research for the further detection of underlying mechanisms of SD.

SD to augment the response of antidepressant medication

In several studies, SD has been applied to potentiate the response to an already existing antidepressant medication in terms of an additional effect, or to reduce the response latency, which in antidepressant pharmacotherapy is usually from 4 up to 6 weeks (see [5]). Although some studies described a better response in patients additionally treated with SD or PSD, the real benefit of additional SD is not clear. This is due to a number of factors that make comparisons between studies very difficult. The studies

Box 1. Sleep deprivation in depression.

Modes of sleep deprivation

- Total sleep deprivation
- Partial sleep deprivation (early/late)
- Rapid eye movement sleep deprivation

Methods to stabilize the antidepressant effect

- Antidepressant medication (predominantly serotonergic)
- Repeated sleep deprivation (two- [total sleep deprivation] or three-times [partial sleep deprivation] per week)
- Sleep deprivation and bright light therapy
- Sleep deprivation combined with sleep phase advance
- Sleep deprivation and repetitive transcranial magnetic stimulation
- Specific neurochemical intervention (state of research), such as pindolol (serotonergic), caffeine (adenosine), flumazenil (GABA) or modafinil (orexin)

vary widely in design, such as in the inclusion criteria, mode of SD treatments, including frequency, duration until follow-up assessment and response criteria. It turned out that subgroups of patients clearly respond, while other patients do not. The reason for those different responses may be due to the underlying neurobiology. Results supporting this suggestion came from a study of Holsboer-Trachsler *et al.*, who provided hints that neurobiological parameters, such as REM latency and HPA axis regulation, may have a major impact on augmentative SD response [89].

Methods to stabilize the SD effect (preventing relapse)

Existing studies examining methods to stabilize the SD effect are discussed in (Box 1) [76,77,90].

Concomitant antidepressant medication

Concomitant antidepressant medication may prevent relapses, as only 53% of medicated responders relapsed in this meta-analysis [3]. While antidepressant therapy may prevent relapses after the recovery night [91], other authors demonstrated that a deterioration of mood is also possible in a number of medicated patients [92,93].

The studies performed on this topic so far do not provide definitive answers as to which patients may benefit from a concommittent medication, nor as to which type of available antidepressant medication may best protect against a relapse. Based on the serotonergic hypothesis of SD, it may be that predominantly serotonergic antidepressants may have a beneficial effect (e.g., [94], see later).

Repeated SD therapy

The results of repeatedly applied SD in the course of antidepressive therapy are still contradictory [4]. In most cases, repeated SD therapy is combined with antidepressant medication. Repeated late PSD at 2-day [92] and 5-day [93] intervals led to a scalariform treatment course (Figure 2). After the immediate effect of each PSD (on average), there was a decline after the recovery night followed by an antidepressant response in the next PSD showing a further amelioration of the depressive syndrome, even after a slight relapse in the following recovery night [92]. It has been shown that at least two SD sessions per week appear to be more effective than only one session per week [95].

The application of two TSDs or three PSDs in 2-day intervals may lead to a stable antidepressant effect lasting over a longer time period [92,96]. Response to a single SD is not generalizable on a series of following SDs in an individual [71,97]. Temporal trends were not observed, except in two studies that reported a gradual decrease of response [10,22], and in one study that described an increase of response to a series of SDs [98].

A reanalysis of data from two studies [99,100] where multiple SDs were carried out revealed that 44% of the patients were consistent responders, and in a further 27%, no response to SD was followed by positive responses. A small group of 9% did not respond after three or more SDs and can be considered as 'real' nonresponders. In rapid cyclers, a pattern of increased responsiveness to repeated SDs was observed, which suggests a possible kindling effect in this group of patients [6].

Combination of SD with bright light therapy

Bright light therapy has consistent antidepressant efficacy in patients with seasonal affective disorder (e.g., [101]). Due to its mechanism of action it is classified – analogue to SD – as a chronobiological therapy. In a first study by Neumeister *et al.,* 2 h of light therapy with 2500 lux in the morning and evening could prevent a relapse into depression at least for 12 days [102]. The same beneficial effect was observed in a randomized controlled study on 115 patients with bipolar depression. The application of 2500 lux of bright light in the morning after SD was able to stabilize the antidepressant response of SD and reduce daytime sleepiness [103]. Benedetti *et al.* demonstrated that history of drug resistance significantly influenced the pattern of relapses and responses to a combined SD–bright light therapy in bipolar patients [104].

Combination of SD with sleep phase advance

The observation that sleep of the recovery night, and also naps in the early morning hours, exert immediate relapses into depression in patients who respond to SD suggests that a critical period in the early morning hours exists where sleep is likely to induce a relapse. In addition, relapse may be related to the release of non-REM sleep. Phase advance of the timing of sleep (sleep from 5 pm to midnight) has been shown to have an antidepressant effect with a latency of 10–14 days [105]. Based on these results, Wehr and Wirz-Justice formulated the 'internal coincidence model for SD and depression', suggesting that the avoidance of sleep during the critical period in the morning hours may be essential for a response to sleep–wake manipulations in depression [106].

With this background, Berger and colleagues conducted a protocol that combines TSD with a phase advance schedule for patients responding to SD [107,108]. After a successful SD, patients were allowed to sleep from 5 pm to midnight. Within the following week the advanced sleep phase was shifted to a normal sleep phase position.

With this strategy they could avoid relapses into depression in 50–75% of the patients who responded to SD. The advantage of this treatment is that in more than half of the patients an immediate improvement in depression could be achieved and stabilized, at least over the observation period of the study [109].

SD & repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation is a relatively new therapy that has shown some antidepressant efficacy. There are two studies that applied repetitive transcranial magnetic stimulation (rTMS) after a SD in depressed patients [110,111]. Eichhammer *et al.* report a prolongation of the SD effect by rTMS in 20 SD responders (controlled by sham rTMS) [111]. By contrast, Padberg *et al.,* who applied ten rTMS sessions with a latency of at least 5 days between SD and rTMS, found an inverse correlation between the effect of SD and rTMS [110].

Specific pharmacologic interventions to augment & stabilize the effect of SD

In the area of neurochemistry, there are a number of potentially promising studies, although they will not be reviewed in detail here.

Serotonergic & adrenergic system

Serotonin in particular is a major neurotransmitter candidate, being involved in sleep and circadian rhythm regulation and the modulation of mood [94].

Total SD enhances the turnover of serotonin (5-hydroxytryptamine [5-HT]) and increases the concentration of 5-hydroxyindoleacetic acid (5-HIAA) during recovery sleep [112]. In depressed patients, tryptophan-stimulated prolactin secretion is enhanced after SD, predominantly in women [113]. Fenfluramine-stimulated prolactin response prior to SD is correlated with subsequent SD response. Following SD, citalopram-induced prolactin response was significantly blunted [114], suggesting a downregulation of 5-HT_{1A} receptors or, alternatively, an acitvation of the tuberoinfunidbular dopaminergic system [114,115]. Furthermore, Kundermann *et al.* report in a recent study, a normalization of serotonergic function assessed by clomipramin challenge in depressed patients after a series of SDs over 3 weeks [116]. Comedication with clomipramine and lithium, which both mainly affect the 5-HT system, intensifies the SD response [117]. In addition, SD may shorten the response latency of treatment with selective serotonin-reuptake inhibitors [118,119].

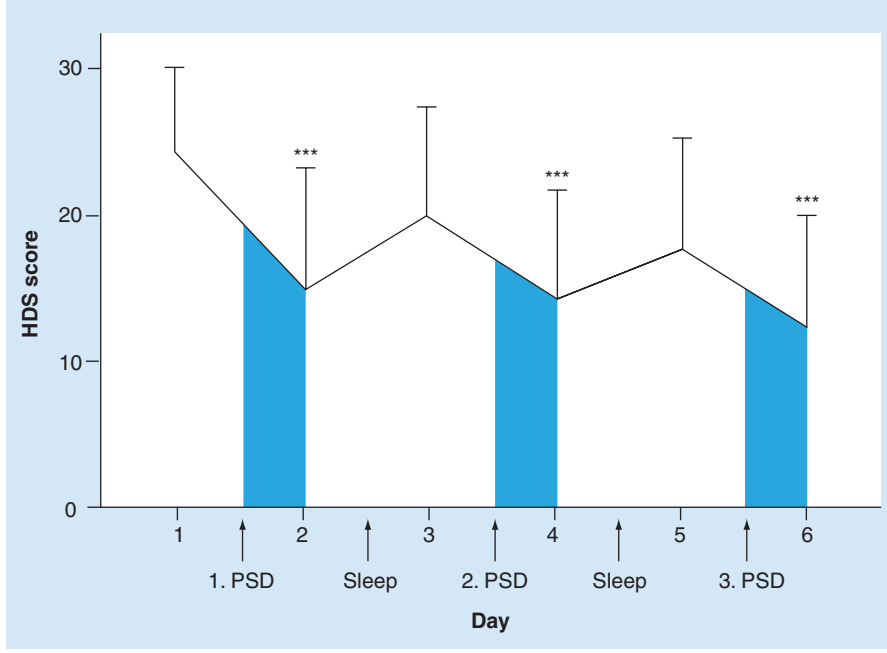

Figure 2. Antidepressant effect of serial partial sleep deprivation.
***p ≤ 0.001.
HDS: Hamilton Depression Scale; PSD: Partial sleep deprivation.
Adapted with permission from [92].

The suggestion that SD affects 5-HT_{1A} receptors is further supported by the finding that SD effects were augmented and sustained with the comedication of pindolol, a β-blocker with 5-HT_{1A} antagonist properties [120].

An important finding is that a functional polymorphism within the promoter of the 5-HT transporter gene is associated with a mood response after SD, at least in bipolar depression [121]. In addition, the 5-HT_{2A} receptor gene polymorphism rs6313 was not associated with the acute, but with a midterm antidepressant response to SD, which became evident after the first recovery night in bipolar patients [104].

However, not all studies consistently show a direct involvement of serotonin in SD effects. Neumeister *et al.* found that the acute antidepressant effect of SD was not reversed by the depletion of tryptophan [122].

In addition, noradrenaline is invoved in SD mechanisms, as it increases urinary catecholamine levels in depressed patients [123]. Furthermore, in animal studies, SD increases synaptic levels of noradrenaline [124], tyrosine hydroxylase and norepinephrine transporter mRNA in the locus ceruleus [125].

Dopamine

From clinical and preclinical studies there are hints that SD and psychostimulants may share similar mechanisms [126]. Both SD and psychostimulants show a rapid onset of antidepressant action compared with established antidepressants, and both only show short-lasting effects.

Dopaminergic activation of the limbic system via D2 and D3 receptors may account for the antidepressant effects of both SD and catecholaminergic psychostimulants [127,128]. In addition, SD improves rigor, akinesia or motor impairment, but not tremor in Parkinson's disease [128]. Furthermore, in functional imaging studies similar metabolic effects of psychostimulants and SD can be observed [127].

The finding that a dopamine reuptake inhibitor prevents the antidepressant effect of repeated SD [129] is unexpected; however, it supports the hypothesis of a dopaminergic involvement in SD.

Studies of polymorphic associations of the candidate genes *DA4* and *DA3* with clinical response to SD have been negative [128,130].

GABA

GABA-A receptors are involved in the regulation of sleep and wakefulness [131]. The alterations of sleep EEG in the recovery night after SD, which are characterized in particular by an improvement of sleep efficiency and an intensification of non-REM sleep [26,49–51,132], widely resemble the effects observed after the application of GABA-A agonistic drugs, such as muscimol or gaboxadol [133]. In addition, sleep endocrine changes, such as increased prolactin [134], and MRI findings after total SD surmise a major participation of the GABAergic system in SD [51,135].

Strong evidence for the hypothesis that the GABA-A system is involved in SD effects comes from the finding that the GABA-A-antagonist flumazenil is able to reverse the sleep EEG changes associated with SD in early morning sleep in volunteers [136]. Based on the results of this study, flumazenil was placebo-controlled applied in a follow-up study in depressed patients in the first hours of PSD, with the aim to suppress the occurrence of

microsleep exactly at the critical time for sleep during SD. The results of this study demonstrated that flumazenil was able to suppress microsleep during SD to a major extent (Figure 3); however, SD response was not differently affected in this study [137].

Other pharmacological manipulations to reduce sleepiness during SD

The adenosine system is a further system that is deeply involved in sleep–wake regulation. Agents that block adenosine 1 (A1) receptors in the brain, such as caffeine, reduce SWS and induce wakefulness. Furthermore, adenosine is considered to be an endogenous sleep factor responsible for the circadian alteration in sleep propensity [138]. The application of caffeine to depressed outpatients during SD kept them awake, but did not influence the SD response [139].

In a single case report, modafinil, another substance with profound vigilance-promoting effects, has been added during SD in a depressed patient who remitted and remained stable under continuing modafinil treatment [140]. In a recently terminated placebo-controlled, randomized study of our group, modafinil was applied to 28 depressed patients during PSD, in order to suppress microsleep. Modafinil was able to suppress microsleep significantly during PSD; however, immediate mood response was not different to the placebo group. The additional treatment with modafinil over 2 weeks induced a significant reduction in REM density, accompanied by a descriptively threefold increase in the antidepressive response rate [141].

This finding, as well as the findings of the application of flumazenil and caffeine during SD, suggests that a mere unidimensional relationship between sleep propensity and the variation of mood during SD does not exist.

Predictors of SD response

Psychopathological & behavioral predictors

The most robust finding concerning the prediction of SD response is the presence of a typical diurnal variation of mood (morning low, evening high) in depressed patients. This has been reported in several controlled studies [22,142–144]. In addition, Reinink *et al.* report that the best TSD results will be achieved in patients with a predominant typical diurnal variation of mood, regardless of whether this typical mood variation is present on the day preceding SD [143].

By contrast, SD in patients with an inverse diurnal variation of mood (evening low) is usually not effective or has negative effects [145]. In a later publication, Reinink *et al.* reported that SD response is correlated with the amount and magnitude of the diurnal mood variation [146]. Besides typical diurnal variation of mood, pre-existing typical sleep disturbance in major depression, including difficulties in falling asleep, frequent awakenings and early morning awakening, is a strong predictor of SD response [22], and observed behaviors of arousal [147] are predictors for SD response. In contrast, tiredness the day preceding SD is associated with SD nonresponse [64]. Furthermore, vital symptoms [7], psychotic features [142] and psychomotor inhibition [148] have been associated with favorable, but also unfavorable, response [4].

In summary, based on these findings it may be concluded that patients with features of typical depression are more likely to respond to SD than patients with signs of atypical depression, such as hypersomnia, tiredness and reduced arousal.

Neurobiological predictors

Reports on sleep EEG parameters as predictors of SD response are not consistent. A shorter REM latency [149,150], an increase of delta sleep ratio [151], a decreased REM density [152] and a more depression-like sleep EEG [52] have been reported as possible predictors of response. In addition, a more intense SWS increase in the recovery night compared with baseline, which may be in line with the delta sleep ratio finding, was related to SD response [153]. However, no difference in sleep EEG parameters between responders and nonresponders was reported elsewhere [154,155]. A recently published study showed that differences in sleep EEG variables between responders and nonresponders strongly depend on the selection and determination of the response criteria [156].

Nevertheless, the majority of results provide suggestions that a sleep EEG that shows characteristic alterations for depression before SD may be associated with a better response.

In addition, characteristic sleep architecture alterations are predominantly found in patients with typical depression compared with depressed patients with atypical symptoms [157]. This could also explain the observation that patients with melancholic or typical features of depression respond better to SD than patients with atypical symptoms.

Neuroimaging

In recent years, predominantly functional neuroimaging presented some results that provided suggestions for a different response to SD.

Several studies performed with fluorodeoxyglucose-positron emission tomography (FDG-PET) or hexamethylpropyleneamine

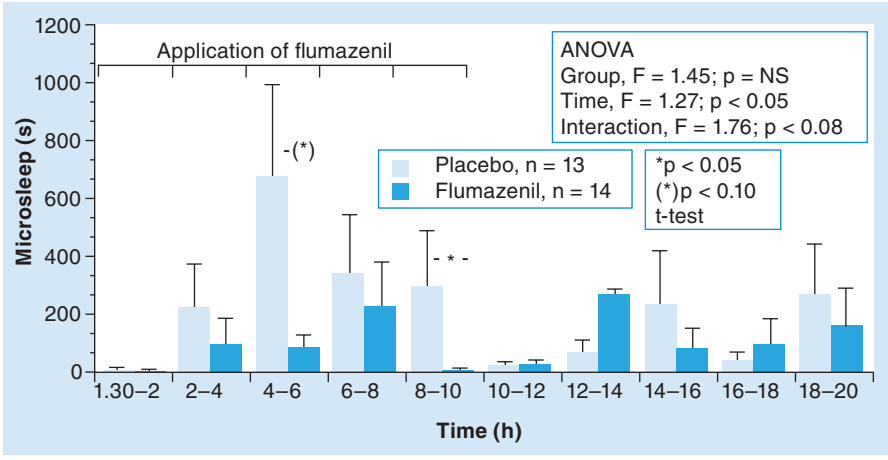

Figure 3. Amount of microsleep in 2-hourly intervals during partial sleep deprivation under flumazenil or placebo application.
NS: Not significant.

oxime single-photon emission computed tomography (HMPAO-SPECT) reported that responders had increased relative localized metabolic activity in the general location of the ventral anterior cingulate cortex and the medial prefrontal cortex compared with nonresponders or normal controls at baseline [158–163].

In addition, in some of these studies clinical improvement was associated with a normalization of the increased metabolic activity in the general area of the ventral anterior cingulate/medial prefrontal regions [158,160–163].

In some studies, clinical improvement correlated significantly with metabolic activity in specific, although different, areas [159,160,164–167].

Furthermore, there is some evidence that responders had a significantly greater displacement of D2 ligand after SD compared with nonresponders, suggesting again that the dopaminergic system may be involved in SD [159].

It is hypothesized that reduced dopamine and serotonin levels may account for the elevated metabolic rate in the anterior cingulate in responders compared with nonresponders at baseline, as the anterior cingulate is innervated by serotonin and dopamine systems [168]. Mobilization of the dopamine and serotonin system could be associated with decreased metabolism in responders after SD [153,168], as the serotonergic system [169] and the dopaminergic system [170] are both enhanced after SD.

Benedetti *et al.* could show that the genotype of the serotonin transporter predicted the response to SD and light therapy in bipolar depressed patients and influenced baseline neural responses to anterior cingulated cortex and dorsolateral prefrontal cortex [104].

Based on the available data, the 'overarousal hypothesis of depression and SD response' has been formulated [171]. It is assumed that depression is associated with a pathological increase in physiological arousal, and SD acts by reducing this aroused state.

Some of the aforementioned predictors of SD, especially the sleep EEG findings with sleep continuity and sleep architecture disturbance (reduced non-REM and increased REM sleep) and the functional neuroimaging findings with elevated baseline limbic activity in depressed SD responders, which is decreased after successful SD comparable with successful antidepressant treatment, support this hypothesis [166].

Expert commentary

The rapid effect of SD on depressive mood within hours is a fascinating experience for the patient, who may have been depressed for weeks or months, and, for the therapist, who still has no conclusive explanation for this rapid relief of depression and, unfortunately, also for the immediate relapse into depression after sleep.

Nevertheless, SD is the only established antidepressant therapy that acts within hours, and therefore, can be applied in patients with treatment-resistant depression with a chance of approximately 50% of seeing an immediate, although temporary, relief from depressive symptoms without major side effects. In addition, even in patients who do not respond to SD, an elevation of mood insomnia, which is frequently accompanied by depression, may be substantially improved at least in the recovery night. The experience of realizing that depression can be lifted and sleep can improve is very important for the further therapy motivation of treatment-resistant depressed patients. In recent years, we have learned much more about the clinical effects of SD. TSD and PSD are efficient. Both can be combined with antidepressant medication, predominantly serotonergic agents, with bright light therapy and with a phase advance of sleep cycles. All these strategies have been able to provide a chance to stabilize the SD response, at least in a subgroup of patients. Furthermore, SD can intensify or accelerate the efficacy of antidepressants.

Based on research findings in the last 40 years, it is clear that the mood-elevating effect is not only due to psychological mechanisms. In depression there is a close relationship between mood variation and sleep, which is related to a number of neurophysiological, neuroendocrine and neurochemical systems in the brain. These systems may be closely involved in the causal effect of sleep and sleep loss on depression.

We know that these different neurobiological systems are deeply influenced by SD. However, it is still not clear what the underlying mechanisms responsible for the immediate response and relapse are. There have already been approaches to specifically influence neurotransmitter systems that are known to be substantially involved in the neurobiology of depression and sleep regulation (e.g., GABA: flumazenil; orexines: modafinil; serotonin: pindolol; and adenosine: caffeine), which increased our understanding of sleep regulation, but did not reveal conclusive results or lead to major progress concerning mood response to SD. Nevertheless, this neurochemical research needs to be intensified in order to understand more about the contribution of these systems to SD response.

Five-year view

There has been ample progress in the knowledge of the neurobiological basis of depression and sleep regulation, which is due to an increased availability of improved methods, such as functional neuroimaging and methods from molecular biology. Data from studies in these areas performed by specialists led to new interesting and stimulating findings, which gave new aspects for further developments in this field.

In particular, preclinical research with new, more sophisticated models of SD related to animal behavior needs to be performed, transferred to clinical research and included in the already existing models of sleep regulation and depression in order to narrow the gap between bench and bedside. Data that arose from neuroimaging (e.g., [163,167]) and genetic research (e.g., [172]) will provide further progress in the understanding of the mechanisms of the effects of SD on mood and daytime functioning.

Predominantly recent findings of genetic factors that may profoundly modulate the effect of antidepressant therapy, such as FKBP-5 [173], should also be evaluated for SD response.

Furthermore, the adenosine and orexin systems and also – as recent data demonstrated – the glutamatergic system, which may also contribute to the acute mood-elevating effect [59], should be more focused on SD than they have been in the past.

Related to these points, an integration of findings from research on the neurobiological basis of major depression related to sleep

regulation, and from research on the action of antidepressant medication, which parallels, at least in part, the effects of SD, is required.

A major problem concerning research on the topic of SD is the dominance of neurochemistry and pharmacology in the treatment of depression. Therefore, there is a lack of interest in this kind of therapy by pharmaceutical companies, and it is difficult to obtain funding for nonpharmacological and non-neurochemical research.

However, the rapidity and the intense modulation of a clinical improvement (and relapse) in response to SD make this a very good tool for testing hypotheses to the understanding of the underlying mechanisms leading to depression, and as a model to develop new, more specific and more rapidly acting antidepressant substances.

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Key issues

- Sleep deprivation (SD) is a powerful antidepressant treatment that shows antidepressant responses within hours in approximately 40–60% of depressed patients.
- Besides total SD, partial SD (PSD; first [early] or second [late] half of the night) has shown comparable antidepressant effects. The effects of late PSD are more evidence-based than the effects of early PSD.
- SD of rapid eye movement (REM) sleep leads to an antidepressant response after several weeks. Owing to the workload of this procedure, it is currently not therapeutically applicable.
- SD can be applied in patients with depressive syndromes in general without major side effects. A contraindication, however, is a history of seizures.
- In bipolar patients, the effect of SD may be even better than in unipolar patients; however, a possible switch into mania has to be taken into account, which can be prevented by the application of lithium and other mood-stabilizing drugs.
- The disadvantage of SD is that the effect is not stable. In more than 80% of responders to SD, a relapse into depression occurred after the recovery night.
- In addition, short naps in the morning, and even very short unconscious episodes of microsleep, may induce relapse or nonresponse.
- An approach to clarify the underlying mechanism of action of SD is to include the current knowledge about the neurobiological disturbance of depression in research, with a focus on neurobiological aspects of sleep and SD.
- SD leads to a transient correction of the depressiogenic sleep EEG in depression (reduced REM-latency and slow-wave sleep, increased REM sleep and REM density), which may lessen the increased hypothalamic–pituitary–adrenal axis acitivity and increase the activity of the somatotropic axis (growth hormone).
- Serotonergic, dopaminergic and GABAergic systems are modulated by SD and may contribute to the SD effects on mood. The instability of mood variation dependent on circadian times also directs to chronobiological effects on the relationship between mood an sleep–wake regulation.
- Strategies to stabilize the antidepressant effect of SD are repeated SDs (twice or three-times a week), SD combined with sleep phase advance in SD responders, SD combined with bright light therapy and the application of antidepressants specifically acting on the serotonergic system – and more specifically, pindolol.
- Predictors for SD response may be diurnal variation of mood, increased tiredness, frequent nocturnal awakenings, early morning awakening, a characteristic sleep EEG for depression (see previous), an un- or less-disturbed function of the hypothalamic–pituitary–adrenal axis and increased metabolic activity of the ventral anterior cingulate.

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