Sleep Deprivation as a Therapy in Psychiatry

7

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Introduction

The antidepressant effect of sleep deprivation (SD) was first described in 1959 in Germany, where Schulte suggested a therapeutic use of SD for depressed subjects basing on anecdotal reports of depressed patients that accidentally stayed awake all night [1]. His collaborators Pflug and Tölle carried out systematic investigations thereof, starting an important research field in psychiatry [2]. Until recently, the observation that the clinical efficacy of SD alone seemed to be hampered by early relapse after subsequent recovery sleep [3] restricted the application of the chronobiological treatment in the context of experimental settings aimed at increasing knowledge about the pathophysiology of mood disorders and discouraged its use in common clinical practice. In recent years, however, different methods for increasing and sustaining the efficacy of sleep deprivation via combinatorial strategies have been studied and the chronobiological intervention could be considered the most rapid antidepressant therapy available today [4]. Little research has been conducted about the use of SD as a therapy for psychiatric disorders other than mood disorders.

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Indication and Contraindication

The principal indication of therapeutic SD is the presence of depression, where an extraordinarily broad response to the chronobiological treatment has been described, irrespective of the syndromal classification. Indeed, an antidepressant effect of SD has been described in endogenous unipolar, bipolar, and schizoaffective depression, reactive depression, depression associated with pregnancy, postpartum and premenstrual dysphoric disorder, depression in the elderly, depression secondary to Parkinson's disease, or schizophrenia [5]. When comparing clinical conditions, the antidepressant efficacy of the chronobiological treatment is higher in endogenous primary depression compared to reactive and/or secondary types (75 % vs. 48 %) [6], and bipolar depressed patients were shown to respond more often than recurrent unipolar ones [7, 8], with the antidepressant effect seeming to be proportional to the patient susceptibility to develop mania. Moreover, the clinical benefit of SD was shown even in drug-resistant depression [9, 10]. Men and women respond equally well. Neither age, number of hospitalizations, earlier treatments, duration of the episode or severity of depression appears consistently related to responsiveness to SD [11].

The influence of SD on mood strictly depends on diagnosis of mood disorder. Indeed, healthy subjects experience either no changes or indeed a worsening of mood after SD [12]. There is little experience regarding its use in other psychiatric disorders. When administered to patients affected

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by obsessive-compulsive [13] or panic [14] disorder the chronobiological treatment led to both improvements or worsening of the symptomatology. While a proven efficacy was showed in schizophrenic patients affected by secondary depression [15], in nondepressed chronic schizophrenic patients treated by 100 h of SD an exacerbation of psychotic symptoms was detected [16]. A recent study by a Japanese group evaluated the effect of SD in subjects affected by posttraumatic stress disorder. The authors suggested that sleep deprivation extinguishes the fear-magnifying effects of memory during sleep, and that insomnia as an acute stress response might provide prophylactic benefits in reducing the development of the disorder [17].

When considering therapeutic SD, a medical examination is suggested before the beginning of the treatment. Indeed, staying awake all night is associated with a nonspecific stress which, although generally well tolerated by healthy people, could unexpectedly precipitate unsuspected medical conditions, e.g., undetected severe cardiovascular diseases [18, 19].

The only known contraindication to SD is the presence of epilepsy, because of the increased risk of seizure induction linked to sleep reduction [20].

Since sleep loss is associated with a marked increase in dopaminergic neurotransmission, caution should be used in administering antidepressant SD to patients affected by Parkinson's disease in which contrasting results have been reported. Indeed, while improvement in motor scores associated with a more prolonged amelioration of depressive symptoms [21] was shown in patients affected by Parkinson's disease after both total [22] and partial [23] SD, in other studies a worsening has been reported after the treatment [24].

For the same reason, the presence of psychotic symptoms should be carefully evaluated, even if no controlled trial has been already done. Indeed, anecdotal reports in literature showed that a worsening of overall symptomatology including an increased extension and pressure of delusions was found after the treatment when SD was administered in delusional depression [25]. Moreover, patients affected by delusional depression showed a larger negative response after recovery sleep even if they had a better response than nonpsychotic depressives to total SD combined with clomipramine [26].

Sleep Deprivation: How Many Hours?

The standard treatment is called "total" SD (TSD) because wake is prolonged throughout the night of treatment. It begins with the extension of daytime wake into the night and lasts about 36 h until the evening of the day after. During this period any napping should be avoided. This is made easier by a nocturnal activity program which however does not seem to have any influence to the therapeutic effect [27]. Indeed, SD has a specific effect which is independent and greater than that of physical exercise [28]. It is still debated if a short nap can block the powerful antidepressant effects of SD, because controversial results have been found. Indeed, while a mood worsening has been shown not only after napping [29] but also even after subjectively unrecognized microsleeps [30], some researchers reported no changes in mood or even a mood amelioration after napping [31]. Moreover, a circadian variation of propensity to relapse into depression as a function of nap timing was suggested (better in the afternoon, but with longer naps in the morning paradoxically less detrimental than shorter ones) [32].

Actually, it is still unclear how many hours of SD are needed to achieve its full antidepressant effect and the minimum amount of sleep restriction needed to obtain any antidepressant effects has not been determined. Over recent years, variants of TSD, such as REM sleep deprivation and partial sleep deprivation (PSD), have been developed.

Selective REM sleep deprivation was suggested to have an antidepressant effect, basing on the observation of REM sleep suppression associated with almost all antidepressants. In 1975 Vogel and colleagues found that depressed patients treated with 3 weeks of REM sleep deprivation by selective awakenings without pharmacological

intervention showed a response comparable to that of imipramine, while a control group of patients deprived of non-REM sleep by selective awakenings did not show any clinical improvement [33]. This finding has not been replicated by the only other study focusing on this topic with a methodologically improved design [34]. The authors compared selective REM sleep deprivation with the same amount of well-balanced awakenings leading to non-REM sleep deprivation in depressed subjects. Even though REM deprivation induced an antidepressant effect in this second study too, the non-REM deprivation group, however, exhibited an even stronger antidepressant response, showing that the antidepressant effects of REM sleep disrupting awakenings was similar to that of nonspecific stage II or slow wave sleep disruption. The use of REM sleep deprivation has always been restricted in the context of experimental settings and it has never been incorporated in clinical practice.

In PSD sleep is allowed during one-half of the night and is called late (LPSD) or early (EPSD) according to the part of the night chosen to be sleep deprived. Schilgen and Tölle [35] deliberately chose the second half of the night for partial SD, introducing LPSD in which patients are woken up at 1:30 a.m. and remain awake till the next evening. They considered it to be decisive to deprive the patients of sleep in the early morning hours because at this time the circadian course of several bodily functions changes direction. Initially, L-PSD was considered as effective as TSD and more effective than EPSD [36], consisting in staying awake until 1:30 then sleeping until 7:00. Thus, it was proposed as the SD method of choice [11]. Regarding the issue of timing for partial SD, subsequent trials specifically addressing the issue of comparative efficacy showed either a better efficacy of late partial SD [37] or similar efficacy of both treatments [38]. According to present knowledge, it seems to be irrelevant whether partial SD takes place during the first or the second half of the night, provided the remaining sleep is equal in duration. Moreover, despite overall response rates being similar, studies directly comparing total and partial SD found indeed TSD to be more effective than partial SD [39].

Response Rates

Cross-sectional data on many hundreds of depressed patients of all diagnostic subcategories show substantial positive responses the day following a TSD [40]. The reported response rates to TSD range from 50 to 80 % of patients, with a mean response rate of 60 % of treated patients across all diagnostic subgroups [40]. Thus, response rates to SD are similar to those observed with antidepressant drugs, but, response to SD becomes clinically relevant in a matter of hours after the beginning of treatment with an improvement which can last for weeks, while antidepressant drugs show longer response latencies. The time course of a positive response to SD usually begins in the second half of the sleep deprived night, but approximately 10–15 % of all patients undergoing SD only react to SD after nocturnal recovery sleep (day-2 responders) [38]. The term "non-response" ranges from lack of any change to extremely negative response [41]. Moreover, lack of antidepressant response to the first SD does not mean that the patient will not respond to further SDs, with about 27 % of not responding to the first night showing positive responses to further SD [40].

Predictors of Response

From a clinical point of view, some patient characteristics seem to be of major importance for the responsiveness to SD. It is one of the most reliable findings in therapeutic SD research that patients with a marked variability of symptoms respond better to SD than those with more stable signs and symptoms. Patients' diurnal variation of mood appears to predict antidepressant response: subjects having the typical diurnal mood fluctuation with an evening mood improvement tend to respond more favorably than those showing a symptomatology worsening in the evening [42]. It was found that average tiredness on the day prior to SD was related to the SD response with patients reporting a relatively low degree of tiredness on the day preceding SD improving more [43], independently from the

severity of depression. Other clinical variables, such as sex, age, age at first onset of illness, duration, or severity of the acute episode have not consistently been related to responsiveness [11].

When patients' sleep characteristics before SD were considered as a predictor of response to the chronobiological treatment, contradictory results were found. In some investigations, patients characterized by short sleep time, low sleep efficiency, and little slow wave sleep showed better response to SD, but other researchers found the opposite or no relationship [44]. Similarly, considering REM-latency and REM-density [44] both positive and negative correlations with response to SD were found. One study concerning spectral analysis of NREM sleep EEG found a correlation between delta sleep and antidepressant effect of SD with a high delta sleep ratio being a positive predictor for response to treatment [45].

Studies on the possible biological predictors of the SD response have yielded disparate results. Response to SD seems to be favored by low peripheral sympathetic activity and high central noradrenergic activity, as indicated by levels of transmitter metabolites in urine and cerebrospinal fluid [11]. An abnormal dexamethasone suppression test (DST) result was found to be a positive predictor of response. Patients who show a trend for normalization of the DST after the treatment have a better antidepressant response [46]. Basal thyroid function was related to the SD antidepressant efficacy with a higher function predicting a better response [47]. Moreover, neuroinflammatory marker production is known to be enhanced in patients affected by a major depressive episode and to affect response to antidepressant drugs [48, 49]. In particular, the response to SD was found to be influenced by interleukine-6 levels: patients characterized by lower baseline levels showed a better response [50]. Indeed, SD influences the nocturnal production of cytokines in depressed patients [51], thus possibly normalizing the disrupted pattern of cytokine production associated with depression [52].

Since the clinical effects of SD are paralleled by specific effects on the brain, a group of brain imaging studies with different techniques considered cerebral cortex activation in specific areas as predictors of response. Responders to SD showed higher relative metabolic rates in the ventral anterior cingulate, medial prefrontal cortex, and posterior subcallosal cortex at baseline than either normal volunteers or depressed patients who did not respond to SD [53], with higher baseline levels being linked with better antidepressant effects.

Finally, the same genetic polymorphisms shown to influence antidepressant response to drugs were found to influence the antidepressant efficacy of SD [54]. In particular, significant associations have been observed with gene variants affecting the promoter of the serotonin transporter [55], the serotonin receptor 2A [56], the catechol-*O*-methyltransferase [57], and the glycogen synthase kinase-3b promoter [58], with a recent research showing a gene–gene interaction between serotonin transporter and glycogen synthase kinase-3b [59].

Short-Term Relapses and Augmentation Therapies

The efficacy of one night of SD as antidepressant treatment was hampered by early relapse after subsequent recovery sleep [3]. Indeed, up to the 80 % of SD-responders relapse, even if incompletely, after the first night of recovery sleep [44] and in the following days patients generally show a trend of progressive worsening with the severity of depression returning to the same levels observed at baseline.

During recent years, many strategies have been developed to sustain the effects of SD over time, preventing the short-term relapses. Serial repetition of TSD was initially studied and was reported to produce more sustained antidepressant effects during treatment but with a delayed (1 month) relapse after treatment in 63 % of responders [60]. Moreover, anecdotal reports of tolerance to treatment in bipolar patients have also been noted [61].

Several studies showed better and maintained clinical responses with the combination of sleep deprivation and antidepressant drugs [3]. In particular, positive interactions were reported with

fluoxetine, paroxetine, sertraline, nortryptiline, clomipramine, desipramine, and amitriptyline. The effect is synergistic: SD hastens the antidepressant action of drugs, or, conversely, drugs sustain over time the transient antidepressant effects of SD [61]. However, negative interactions were observed with trimipramine and amineptine [62, 63]. Lithium salts, the mainstay for the treatment of bipolar disorder, as well have been found to sustain over time the antidepressant effect of SD. This augmentation effect was found not only when lithium was used as a long-term treatment but different studies showed that starting lithium in previously untreated patients prolonged the effect of sleep deprivation for at least 30 days [64]. Lithium salts not only sustain response to SD, but it enhances it as well, probably by overcoming the effect of unfavorable genetic predispositions which affect the functioning of the serotonergic system [65].

Finally, antidepressant sleep SD has been successfully combined with other chronobiological treatment such as bright light therapy (BLT) or sleep phase advance (SPA). Early studies on SD combined with BLT showed that the effectiveness of SD became more significant when BLT was conducted in the morning [66]. Moreover, not only the exposure to BLT during and after wake therapy (TSD) was shown to stabilize the antidepressant effect of both partial [67] and TSD [68, 69], but also a more prolonged improvement of responders seem to be linked to the use of BLT during SD [70].

Early studies on SPA employed a 1-week schedule: after SD, bedtime started at 5 p.m. on the first recovery night and was shifted (delayed) daily by 1 h until reaching a more conventional bedtime of 11 p.m. [71–73]. Recent studies focused on a 3-day schedule in which the bedtime was delayed daily by 2 h until the conventional bedtime. This 3-day schedule was found to successfully prevent relapse as well as the 1-week schedule [74, 75].

In summary, Wirz-Justice et al. [4] concluded that relapse after SD can be prevented by concomitant medication, BLT, and/or SPA following SD, and combinations of these interventions can also prolong response duration. Combined (SD + SPA + BLT) chronobiological interventions have been demonstrated to have a good efficacy when added to ongoing antidepressant drug in depressed patients. Indeed, Wu and colleagues showed that the antidepressant efficacy of the three established circadian-related treatments as adjunctive treatment to lithium and antidepressants was more rapid and robust than the one of the drug treatments [74]. Recently, the combination of SD, SPA, and BLT as adjunctive treatment were shown to be effective also in drug-resistant depressed patients [10].

Our group has developed a treatment schedule which has been shown to prevent short-term relapses. It combines repeated SD with BLT and lithium salts [68]. It consists of three cycles of 36 h SD separated by 1 night of recovery sleep. Inpatients stay awake from 7 a.m. until 7 p.m. the following day, during the first, third, and fifth day. Then, they are allowed to sleep during the night of the second, fourth, and sixth day. The alternation of 3 nights of undisturbed sleep means that the period of sleep–wake cycle is enlarged from the usual 24 h length to 48 h. Moreover, patients are administered BLT during the SD night at 3 a.m. and in the morning after recovery sleep between 8 and 9 a.m. Lithium salts administration, if not already ongoing, is started at the beginning of the chronotherapeutic procedure. This combination treatment was found to have an antidepressant efficacy even in drug-resistant bipolar depression [9], with an acute antidepressant response in the 44 % of patients who did not show a response to antidepressant drug.

Safety

Several studies have confirmed the safety of SD which has very few side effects. However, worsening of depressive symptoms occurs in 2–7 % of therapeutic SDs. We note that a paradoxical acute worsening of suicidal ideation and/or attempts, and of completed suicide, is possible with all antidepressant treatments and every clinical psychiatrist knows that antidepressant treatments may transiently increase these risks before leading to the remission of the depressive syndrome and

of the depressive cognitive distortions (hopelessness/helplessness) linked with suicidal ideation. Current knowledge about antidepressants and suicidality suggests a transient increase in children, adolescents, and young adults under age 25; no transient suicidality effect in adults aged 25–64 and a protective effect in over 65-year-old people [76]. Even if there is no reason to think that SD should be an exception to this rule, no report associated therapeutic SD with a worsening of suicidality [5]. Moreover, two studies described rapid amelioration of depressive cognitive distortions after SD alone [77] or combined with SPA [5].

Independent of depression, SD can provoke epileptic seizures in predisposed persons. Other side effects are headaches and gastrointestinal complaints [44]. The most common and obvious adverse effect is daytime sleepiness with a degree of sleepiness showing a high individual variability.

In bipolar patients undergoing SD, there have been occasional reports of switches into hypomania or mania with approximate 5 % switch rate into mania and 6 % into hypomania. The switch rate is influenced by a concomitant use of drugs: it is reduced by mood stabilizers and increased to 10–15 % by antidepressant drugs. When treating rapid cycling bipolar depressed patients, a high rate of manic switches is expected after SD, as well as after any antidepressant medication [78]. In conclusion, in bipolar depressed patients treated by SD, the mania switch rate is similar to those observed with SSRIs and placebo, and lower than those reported with tricyclic antidepressants [79] used as antidepressant treatments, and much lower than those reported (10–29 %) in bipolar patients receiving antidepressant drugs as maintenance treatment [80]. It should be noted that the severity of mania induced by TSD is mild or moderate in the majority of patients. Indeed, one third of switched patients return to euthymia after a good night of recovery sleep (facilitated by benzodiazepines), without the need of any further treatment during the next days, and less than half of the patients need to combine antipsychotic medication with mood stabilizers to get out of mania [81].

Bipolar patients can be affected also by mixed states which are characterized by the simultaneous presence of depressive and manic symptoms pertaining to both depression and mania are simultaneous. Current guidelines on diagnosis and treatment compare mixed states to bipolar mania, and suggest to avoid antidepressants because they may worsen intraepisodic mood lability [82]. In cases of a mixed episode with prevalent depressive symptoms, the administration of antidepressant SD may precipitate mania.

When Panic Attacks disorder is comorbid with Mood Disorder, the anxiety disorder will be expected to worsen during the night of sleep deprivation without any negative influence on the antidepressant effect. Patients should be informed about this condition [81].

Mechanism of Action

SD is a complex intervention and it should be considered multi-target in nature. Thus, the mechanisms explaining its antidepressant effect can be looked for on many levels. Sleep deprivation differentially affects neurotransmitter systems, including serotoninergic, cholinergic, noradrenergic, and dopaminergic function [83–85]. Biological factors affecting the activity of these pathways, such as genotypic variants [53, 55, 56, 86], basal neurotransmitter levels [87], or the extent of receptor occupancy [88], affect the clinical response thus confirming a critical role for changes in monoaminergic neurotransmission in the clinical effect of SD. One of the most consistent findings comes from data showing that SD enhances serotonergic function, similar to many antidepressant medications [89] both in humans [90] and animals [91, 92]. Moreover, a functional polymorphism within the promoter of the serotonin transport gene, serotonin transporter-linked polymorphic region, may influence antidepressant response to SD [55].

SD increases the levels of thyroid hormones [93, 94], and interacts with emerging specific targets for the treatment of mood disorders such as glycogen synthase kinase 3-β [58] and glutamate [95]. Indeed, SD was found to alter glutamate

metabolism with a reduction in cortical glutamate concentrations paralleling clinical response to the treatment [95]. Remarkably, the effects were detected in the same cerebral area, such as the dorsal anterior cingulate cortex, where changes in 5-HT function were found to influence neural responses to depressive cognitive stimuli [53]. According to this finding, glutamate neurotransmission and its interaction with monoamines could have a role in the rapid antidepressant effects of SD. Research in animal models showed that SD promoted a synaptic potentiation increasing the inhibitory phosphorylation of GSK3-β [96] which is an essential element of the Wnt/beta-catenin pathway and plays major roles in neurodevelopment and in regulation of neuronal plasticity and cell survival [97]. Moreover, GSK3-β is supposed to be involved in the mechanism of action of lithium and serotonergic antidepressants and its Drosophila orthologue SHAGGY was found to be implicated in the regulation of the molecular clock located in the suprachiasmatic nucleus of the hypothalamus [98]. A promoter single nucleotide functional (greater activity of the T allele) polymorphism of GSK3-β (−50 T/C; rs334558) was found to influence the response to SD. Indeed, bipolar depressed homozygote carriers of the C allele showed a better mood amelioration after SD and a relapse similar to the other subjects after recovery sleep [58]. Moreover, recently a gene–gene interaction between rs334558 and serotonin transporter gene in influencing antidepressant response to SD was found [59].

SD can influence the activity of the suprachiasmatic nucleus of the hypothalamus by modifying vigilance state transitions and sleep states [99]. Changes in sleep homeostasis have been hypothesized to play a major role in the mechanism of action of sleep deprivation [40]. According to the recent "synaptic homeostasis hypothesis" of sleep [100], the antidepressant action of SD could be related to the marked changes in neuronal connectivity leading to major changes in brain metabolism and function caused by the chronobiological treatment. Moreover, recently SD was found to influence the expression of some genes of the biological clock which are known to contribute to the homeostatic aspect of sleep regulation [101]. Since it is hypothesized that a subset of patients with severe depression who experience circadian rhythm abnormalities, including mood, sleep, hormonal, and/or temperature regulation, have a state-related defect in clock gene machinery, SD could be supposed to have an antidepressant effect by stabilizing clock gene machinery [102].

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