Sleep Deprivation in Mood Disorders

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Key Words

Sleep deprivation • Antidepressant • Bipolar disorder • Major depression • Mania • Light therapy

Abstract

Growing clinical evidence in support of the efficacy and safety of sleep deprivation (SD), and its biological mechanisms of action suggest that this technique can now be included among the first-line antidepressant treatment strategies for mood disorders. SD targets the broadly defined depressive syndrome, and can be administered according to several different treatment schedules: total versus partial, single versus repeated, alone or combined with antidepressant drugs, mood stabilizers, or other chronotherapeutic techniques, such as light therapy and sleep phase advance. The present review focuses on clinical evidence about the place of SD in therapy, its indications, dosage and timing of the therapeutic wake, interactions with other treatments, precautions and contraindications, adverse reactions, mechanism of action, and comparative efficacy, with the aim of providing the clinical psychiatrist with an updated, concise guide to its application.

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Introduction

Sleep deprivation (SD) is a core component of psychiatric chronotherapeutics, defined as the controlled exposure to environmental stimuli that act on biological rhythms in order to achieve therapeutic effects in the

treatment of psychiatric conditions [1]. The use of SD in everyday psychiatric practice is fairly new, and is almost exclusively restricted to the treatment of mood disorders. These techniques include manipulations of the sleep-wake rhythm (such as partial and total SD and sleep phase advance) and of the exposure to the light-dark cycle (light therapy, dark therapy) [2], and have been developed either directly from neurobiological models of behavior, as in the case of light and dark therapy, or by monitoring rapid antidepressant effects after prolonged wake, as in the case of SD [3].

After the initial descriptions of its rapid and powerful effects [4], the use of SD has long been restricted to experimental settings, in the context of research aimed at studying the mechanisms of action of this treatment in order to deepen our knowledge on the pathophysiology of depression [5]. Application in common clinical practice was discouraged by the early observation that SD is acutely followed by an abrupt mood improvement after a single night awake, but that a depressive relapse is expected after the restoration of normal sleep [6]. In recent years, however, something changed: (1) increased neurobiological knowledge on the functioning of the biological clock led researchers to hypothesize that internal timing is a key factor to mental health [7], and triggered increased interest in treatments directly targeting its basic functioning [8], and (2) the continuous development of new clinical strategies for the chronotherapeutic treatment of depression and their combination (e.g. SD plus light therapy) or their association with antidepressant drugs and mood stabilizers led to long-term remissions [9].

Thus, while many papers reviewed data on the effects of SD and, in some cases, proposed it as an experimental model of antidepressant treatment [2, 6, 10–15], few authors reviewed evidence on its clinical use against depression [1, 9, 16, 17]. The aim of the present review is to provide an updated concise clinical guide on SD in the treatment of mood disorders.

Place of SD in Therapy

The magnitude of improvement after one night of SD is often equal to that observed after 6 weeks of antidepressant medication, for example, a 50% or greater reduction in the scores on the Hamilton Rating Scale for Depression (HRSD) and a final HRSD <9 [13]. Mainly developed in European countries over the last 5 decades, this technique evolved both from empirical observations of impressive clinical changes following random exposure to environmental stimuli (e.g. immediate mood improvement in depressed patients deprived of sleep by chance) [18], and from neurobiological models of behavior tested in preclinical experimental settings [19].

The reported response rates are similar to those observed with antidepressant drugs, ranging from 50 to 80% of treated patients [1], but with the difference that the response becomes clinically relevant in a matter of hours after the beginning of treatment (i.e. the day after) without the long response latencies usually associated with antidepressant drugs [1, 6, 15].

The therapeutic target is the broadly defined depressive syndrome. While the majority of normal subjects experience no changes or a worsening of mood after SD [20], patients affected by primary or secondary major depression usually experience some degree of improvement [16]. Thus, positive antidepressant effects of SD have been reported in endogenous, reactive, unipolar, bipolar, secondary, and schizoaffective depression [16], in depression in the elderly [21] and secondary to Parkinson's disease [22] or schizophrenia [23], and in depression associated with pregnancy and postpartum [24] and premenstrual dysphoric disorder [25].

Nevertheless, a diagnostic criterion should be used to define indications because, when directly comparing psychiatric conditions, better effects have been observed in endogenous primary depression compared with reactive and/or secondary depression [26], and in the treatment of bipolar disorder compared to primary depressive disorder [27]. Age is not an issue [28, 29].

Based on the available literature, the primary indication for antidepressant SD treatment should then be a major depressive episode in the course of bipolar disorder, but the clinical psychiatrist can use this technique in all depressive conditions based upon clinical need.

Dosage and Timing of the Therapeutic Wake

Duration of Wake

It is still unclear how many hours of SD are needed to achieve its full antidepressant effect. A typical antidepressant SD treatment begins with the extension of daytime wake into the night, and lasts about 36 h until the evening of the day after, when sleep is again allowed (so-called 'total' SD because wake is prolonged throughout the night of treatment). Given the simple schedule and the powerful effects in the absence of side effects, the effects of total SD are best documented in the literature compared to those of other sleep restriction modalities [13, 30].

During this extended wake, a turning point of mood common to all patients has not been demonstrated, but existing studies suggest that the antidepressant effects of SD do not occur before the end of the night awake [31] and become clinically evident when the patient is exposed to daytime light, after the night awake, or earlier during the night, if the SD is carried out in bright light [32].

During the prolonged wake, it is suggested that the patients remain awake without napping, in order to avoid the depressive relapse that follows recovery sleep, but while some researchers reported a mood worsening after napping [33] or even after subjectively unrecognized microsleeps [34], others did not, or even reported a mood amelioration after napping [35], or suggested a circadian variation in the propensity to relapse into depression as a function of nap timing (worse in the morning, but with longer naps paradoxically less detrimental than shorter ones) [36]. It is then still debated if a short nap can block the powerful antidepressant effects of SD. Available data suggest that this interaction may be linked with yet undefined individual characteristics (possibly including the individual turning point of mood) and that a full response to SD can well occur independent of napping.

This hypothesis is sustained by the observation that SD can be limited to a part of the night, and nevertheless obtain clear antidepressant effects in as much as 75% of treated patients (so-called 'partial' SD because sleep is allowed during one-half of the night) [37]. The observation

that partial SD late in the night was followed by response rates similar to those obtained after total SD led to propose it as the SD method of choice [38], but the issues of efficacy, timing and stress are yet debated [17]. Despite similar overall response rates, studies directly comparing total and partial SD found indeed total SD to be more effective than partial SD [39]. Moreover, it is not self-evident that to be awakened during the second half of the night (e.g. at 02:00–03:00 h in the morning) and stay awake until the following evening is less stressful than spending the whole night awake, and studies assessing the degree of stress linked with the different treatment modalities are lacking. Regarding the issue of timing for partial SD (first or second part of the night), trials specifically addressing the issue of comparative efficacy showed either that late partial SD was more effective than early partial SD, thus suggesting that both time and duration of sleep affected treatment response [40]; or that early and late partial SD had similar efficacy, thus suggesting that sleep reduction as such, and not the time at which it takes place, correlated with the therapeutic effect of SD [41].

The minimum amount of sleep restriction needed to obtain antidepressant effects has not been determined, but very short SD schedules, such as a 2-hour sleep restriction in the middle of the night, have been shown to produce little clinical effect [39].

Finally, the early hypothesis that the therapeutic effect of SD is linked with the deprivation of rapid eye movement (REM) sleep is now questioned given that the early report of better antidepressant effects in selective REM sleep-deprived patients [42] has not been replicated by a recent comparative study which showed that the antidepressant effect of REM sleep-disrupting awakenings was similar to that of aspecific stage II or slow wave-sleep disruption [43]. Moreover, despite its similarity with the REM sleep-suppressing effect of some antidepressant drugs [44], selective REM SD was never used in clinical practice, and its specific usefulness thus remains hypothetical.

Repetition of Treatment

Repetition of treatment is allowed, and can lead to progressively better effects. Our group developed a treatment schedule based on repeated total SD, three times a week, resulting in a lengthening of the sleep-wake period from the usual 24 to 48 h [1, 45–52]. Each SD cycle is composed of a period of 36 h awake, and on the 1st, 3rd and 5th day, patients are totally sleep deprived from 07:00 h until 19:00 h of the following day. They are then allowed to

sleep during the night of the 2nd, 4th and 6th day. SD is carried out in normal ambient light, but patients are administered light therapy during the SD night, to counteract sleepiness, and in the morning after recovery sleep, half an hour after awakening, between 8 and 9 a.m. from day 1 to day 7.

Many other schedules for repeat treatment have been proposed: e.g. partial SD repeated once a week for 3 weeks [53], or 3 times a week [54], or twice a week for 2 weeks [55], or 3 times a week for 2 weeks [56], or 5 times at 5-day intervals [57], or 6 times at 4- to 5-day intervals [58]; or total SD twice a week [59], or twice a week for 3 weeks [60, 61] or for a month [62], or twice a week followed by partial SD twice [63], and so on. Repeated total SD once a week has also been proposed as a prophylactic treatment, to sustain response and prevent relapses [64, 65].

Direct comparisons, however, are very scarce. In a crossover trial, the comparison of partial SD once versus twice a week for 2 weeks failed to find a difference in the magnitude of the antidepressant effects [66]. Given, however, that response to a single SD is not generalizable to a series of SDs in an individual [60], a patient may well not respond to the first SD and respond to the second one, and this pattern is of high clinical importance. Evaluation of the comparative efficacy of these different treatments is then prevented, and what is still undefined, and highly needed in a clinical perspective, is a reliable assessment of a dose-response relationship between amount, timing and repetition of wake therapy and extent and duration of the clinical antidepressant response.

Recovery Sleep and Relapse

Obviously, wake cannot last indefinitely, and SD ends with recovery sleep. In reported trials, recovery sleep is free and undisturbed, with the patient choosing the most appropriate bedtime and waking up when the night sleep ends spontaneously. Actigraphic evidence showed that after total SD patients significantly anticipate bedtime and sleep onset, and sleep more and better than before treatment (when sleep was usually disturbed by depressive insomnia) [52].

According to early descriptions of the clinical effects of SD, relapse is expected in the morning after awakening from recovery sleep, even when a complete response had been achieved the evening before [6, 16]. The depressive syndrome usually manifests itself with a lower degree of severity than before treatment, and some objective improvement in mood and cognition is maintained [67, 68], but in the following days, patients tend to show progressive worsening and the severity of depression returns to

the levels observed at baseline. Recovery sleep does not necessarily lead to relapse on the first day after SD [17], and a small subgroup of patients (10–15%) shows an atypical improvement on the day after recovery sleep instead of improving immediately after their night wake [41]; nevertheless, in the following days, mood is expected to progressively deteriorate [6].

Repetition of the treatment leads to a typical sawtooth pattern with repeated ameliorations after SD and repeated relapse after recovery sleep [47], with little net benefit at the end. The trend toward amelioration due to incomplete relapses, when present, is expected to reverse within a few weeks after a regular restoring of the usual 24-hour sleep-wake cycle, and in the absence of combined treatments only a 5–10% of bipolar depressed responders achieve sustained remission from their depressive episode [46, 48].

Interactions with Other Treatments: The Need for Combined Antidepressant Strategies

Considering the almost inevitable risk of early depressive relapse after SD treatment, combined antidepressant and mood-stabilizing strategies are needed to achieve sustained clinical effects.

Total or partial, single or repeated antidepressant SD has been successfully associated with the selective serotonin reuptake inhibitors fluoxetine [45], paroxetine [29, 69, 70] and sertraline [71, 72], the dopaminergic amineptine [49], the mixed serotonergic-noradrenergic tricyclic antidepressants amitriptyline [58, 66] and clomipramine [73–77] and the noradrenergic tricyclic nortriptyline [78]. The effect is synergistic: SD hastens the antidepressant action of drugs or, conversely, drugs sustain the transient antidepressant effects of SD over time. Whichever the interpretation, the clinical trials consistently show that a stable clinical euthymia is achieved by the majority of patients [1, 2, 10]. A negative interaction has only been reported when SD was combined with trimipramine [79], which shows in vitro DA antagonistic properties [80]. Combined SD and antidepressant treatment not only improves the depressive syndrome, it also exerts a beneficial effect on overall quality of life; partial SD combined with sertraline caused a faster improvement in WHOQoL scale scores than sertraline monotherapy [71].

Lithium salts are the mainstay of the treatment of bipolar disorder, and sustain the antidepressant effects of SD as well [81, 82]. Continuing lithium in the usual therapeutic range leads to sustained remission over the

months, and stable euthymia is then obtained in the majority of patients without the need for other psychotropic drugs [47, 48, 50]. Lithium not only sustains 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 [83].

Finally, to enhance and sustain its effects in the days immediately following treatment, SD has been combined with other chronotherapeutic techniques. Several independent trials consistently reported synergistic effects of the combination of SD with light therapy [48, 50, 84, 85] and/or subsequent sleep phase advance [77, 86–89].

Precautions and Contraindications

Delusional Depression

The presence of psychotic symptoms should be carefully evaluated. Major depressive episodes with psychotic features constitute a severe disability, hence the necessity to obtain a rapid amelioration of symptoms, and SD could be a good candidate to pursue this aim. Literature evidence is sparse, however, and suggests caution in administering SD to psychotic depressed patients. One group reported that depressives with psychotic features reacted more favorably than nonpsychotic depressives to total SD combined with clomipramine, but also that more marked negative responses were observed after recovery sleep (either unlimited or partial sleep) in psychotic versus nonpsychotic depressives [90, 91]. Anecdotal reports on delusional depressed patients treated with SD showed that in some cases an ‘increased intensity of drives’ after SD was paralleled by a worsening of psychotic symptoms [92], that 1 patient switched polarity after combined SD and tricyclic medication, while another, treated with combined SD and neuroleptics, showed a moderate improvement [93] and that the average response in 3 psychotic depressives treated with total SD and placebo was positive [94]. Our group treated 5 patients with total SD, in the absence of concomitant drugs, and observed a worsening of overall symptomatology including increased extension and pressure of delusions [95]. In the absence of balanced controlled trials, no definite conclusion can be drawn on this topic, but caution and a careful antipsychotic strategy, possibly including combined medications, is suggested by the available literature.

Mixed States

‘Pure’ depression and mania are not the only psychopathological conditions that affect bipolar patients, who

may also experience mixed states in which symptoms pertaining to both conditions are simultaneous. The current clinical management of these episodes relies on the classical *ex adjuvantibus* medical reasoning more than on complex psychopathological discussions: mixed states show good response to antimanic treatment, with particular sensitivity to antiepileptic mood stabilizers [96]. Current guidelines on diagnosis and treatment assimilate mixed states to bipolar mania and suggest to avoid antidepressants because they may worsen intraepisodic mood lability [97].

In case of a mixed episode with prevalent depressive symptoms, the administration of antidepressant SD will precipitate mania. Given that mania can be a less threatening condition than a psychotic mixed state, this strategy has been suggested as useful in clarifying diagnostic conundrums and define treatment options in clinical conditions such as puerperal psychosis, when categorical diagnosis is uncertain and rapid treatment is needed [98]. However, given that sleep loss could have a causal role in the development of postpartum psychosis [99], caution is strongly suggested in using this approach.

Medical and Neurological Conditions

SD is a stressor [100], and should thus be preceded by a medical examination aimed at ruling out the presence of medical conditions that can be worsened by even low degrees of stress. The unspecific stress associated with staying awake all night could unexpectedly precipitate unsuspected medical conditions, e.g. undetected severe cardiovascular diseases [101, 102].

Sleep is a potent activator of interictal epileptiform discharges, and SD is a trigger of epileptic seizures [103]. The relationship between changes in synaptic efficacy during the sleep-wake cycle, epilepsy [104] and the therapeutic effect of SD [5] is still unclear, and there is a lack of data about the possible efficacy of SD in patients treated with antiepileptic drugs at therapeutic levels. A significant association was reported between antidepressant response to SD and to a trial of carbamazepine, but it is unclear whether this relationship was based on antidepressant response to any agent or was specific to carbamazepine [105].

In Parkinson's disease, contrasting results have been reported. A higher lifetime sleep duration has been associated with a higher risk of developing this disease, while rotating shift work and sleep loss had a protective effect [106]. Probably due to the marked increase in dopaminergic neurotransmission associated with SD, sleep-deprived patients affected by Parkinson's disease temporarily

improved their motor scores after total [22, 107, 108] or partial SD [109], and the improvement in motor symptoms was associated with a more prolonged amelioration of depression [110]. In subgroups of patients, however, a sleep benefit and a worsening after SD have been reported [111], and caution should thus be used in administering antidepressant SD to patients with Parkinson's disease.

Partial SD has been successfully used to treat depression during pregnancy, when the use of psychotropic drugs is discouraged [24]. A history of sleep disruption in the latter stages of pregnancy has been associated with the development of postnatal blues [112], but it is unclear whether sleep perturbation, with its associated changes in the sleep-immunity relationship [113, 114], has an etiological role or is an early symptom of the depressive syndrome which fully develops after childbirth. In the absence of clear-cut evidence, caution should be exerted in administering SD, as any other stressor, to pregnant women.

Adverse Reactions

Sleepiness

The most common and obvious adverse effect of SD is daytime sleepiness, and patients treated with SD should be advised not to engage in dangerous activities which require attention and concentration (e.g. driving a car). The degree of sleepiness shows high individual variability, and anecdotic reports and lay observations described patients who could continue their daytime job activities despite having stayed awake all night due to an antidepressant SD treatment [115]. Considering the large literature about sleep loss and the increased risk of accidents, however, patients should be protected from these easily avoidable risks [1].

Recently, the combination of wake-promoting substances, such as flumazenil, has been proposed to reduce sleepiness and to improve antidepressant response by suppressing microsleeps [34, 116]. Carrying out the treatment in a hospital setting, as in most reported trials, can, however, prevent the consequences of this unavoidable adverse effect.

Manic Switches

In euthymic patients affected by bipolar disorder, abrupt changes in the sleep-wake rhythm can trigger mania through a self-reinforcing mechanism of sleep loss and progressive mood improvement, which leads to the

typical increase in activity, reduced need for sleep, and eventually the full manic syndrome spinning out of control [117, 118]. Indeed, when treating rapid-cycling bipolar depressed patients a high rate of manic switches is expected after SD [119] as well as after any antidepressant medication.

In non-rapid-cycling patients affected by bipolar disorder type I, very low switch rates have been observed in reported trials. In an early review on the effects of SD in depression [6], a 30% switch rate was reported, based on 10 studies published between 1974 and 1982. When examining more recent studies on the effects of SD, switches into mania disappear from literature reports except when considering rapid-cycling bipolar patients [120]. It is possible that the widespread diffusion of lifetime mood-stabilizing therapeutic strategies could have contributed to this favorable evolution over the decades. Regarding the bipolar rapid-cycling condition, the spontaneous occurrence of SD before switches into manic phases was observed in 13/15 rapid-cycling bipolar patients, while therapeutic SD caused 7/9 drug-free depressed rapid cyclers to switch into mania [119]: no doubt that the administration of therapeutic SD in this particular subgroup of patients causes the same switch rate into mania that is expected to occur naturally with spontaneous SD in the illness course.

On the other hand, in 206 bipolar depressed inpatients treated with serial repetition of total SD, we observed a 4.85% switch rate into manic phase, and a 5.83% switch rate into hypomanic phase [120]: these switch rates are closely similar to those observed with selective serotonin reuptake inhibitors and placebo, are lower than those reported with tricyclic antidepressants [121] and are much lower than the reported 10–29% manic switches in patients affected by bipolar disorder and administered maintenance treatment with antidepressants [122, 123]. Moreover, the severity of mania was rather mild or moderate in the majority of our patients, and less than one half needed to combine antipsychotic medication to mood stabilizers to return to euthymia: since manic symptoms appeared during hospitalization, patients were immediately administered a medication, and restoration of night sleep with intravenous benzodiazepines resulted in a rapid resolution of manic symptomatology in one third of the patients; another third developed a manic phase which resolved within 1 month with mood stabilizers, and roughly the last third developed a full manic episode with psychotic features and needed neuroleptic medication. All patients with hypomanic symptoms returned to euthymia with lithium salts and benzodiazepines alone [120].

Two factors should be considered to explain this good prognosis of mania induced by therapeutic SD. First of all, this ‘mania’ does not fulfill the DSM-IV temporal criterion of mania because symptoms are expected, observed and treated at their very onset, and the clinical characteristics of the ‘episode’ can thus not be compared with those reported in trials on bipolar mania. Second, the clinical situation is very different from that of patients who have already completed the closed-loop feedback between sleep loss and behavioral activation [117, 124–126]: clinical evaluations of the relationship between sleep loss, perturbation of the activity-rest cycles and light-dark exposure, and manic psychopathology, consistently confirmed that at the beginning of mania (but not thereafter), sleep loss directly triggers and augments mania [127], and sleep and dark exposure rapidly stop it [128].

The risk of a manic switch after therapeutic SD thus seems to be low, preventable, and with easily treatable consequences, and should not be regarded as a contraindication except in the case of rapid-cycling patients when, based on previous history and current evaluation of the clinical picture, the psychiatrist and his patient consider the risk of mania to overcome the antidepressant benefits of therapeutic SD.

Mechanism of Action

Despite the fact that the literature tends to emphasize the specificity of drug actions, defined as the exclusive interaction with a single critical target, many effective treatments target several mechanisms and a multitarget approach to treatment could be better suited for a multifactorial illness such as depression [129]. The mechanism of action of SD is multitarget in nature, and involves multiple and powerful effects on known targets for psychiatric antidepressant treatment [5]. Most probably, all these mechanisms contribute to the clinical outcome and help to explain the impressive rapidity and efficacy of this technique.

Regarding monoamines, converging evidence from preclinical studies and in vivo studies in depressed patients showed that SD potentiates neurotransmission based on serotonin [130, 131], noradrenaline [132–134] and dopamine [11]. Biological factors affecting the activity of these pathways, such as genotypic variants [51, 135–137], basal neurotransmitter levels [138], or the extent of receptor occupancy [139], affect the clinical response, thus confirming a critical role for changes in monoaminergic neurotransmission in the clinical effect of SD.

Moreover, SD increases the levels of thyroid hormones [140, 141], and interacts with emerging specific targets for the treatment of mood disorders such as glycogen synthase kinase 3 β [142], glutamate [143] and the sleep-related mechanisms which regulate synaptic homeostasis [144].

The clinical effects of SD are paralleled by specific effects of SD on the brain. An impressive group of brain-imaging studies with different techniques consistently showed that the antidepressant response to SD is associated with specific functional and metabolic changes in specific brain areas. In particular, major changes are observed in the general location of the ventral/anterior cingulate cortex and medial prefrontal cortex, with responders to SD showing increased relatively localized metabolic activity compared with nonresponders or normal controls at baseline: the higher the baseline levels, the greater the decrease induced by SD and the better the antidepressant effect [13, 14, 72, 145]. The metabolic changes after SD are paralleled by a decrease in perfusion of the cingulate [146] and amygdala [147], which is specific of response to treatment, by changes in spectroscopic correlates of glutamatergic activity in the cingulate [143] and changes in neural correlates of brain activity in response to tasks targeting the typical depressive negative cognitive distortions [51].

These results are consistent with measurements of metabolic activity in major depression at baseline and after recovery, which showed higher metabolic rates in the perigenual cingulate at baseline and a decrease after pharmacological treatment that was proportional to the clinical amelioration [148, 149]. In a pivotal study, similar changes were obtained in the same subjects with a single SD and with a 1-month paroxetine treatment course [150].

Comparative Efficacy

Acute response rates to SD range, depending on reported estimates, from roughly one half to three quarters of patients, similar to those reported for drug treatments [2, 17]. Given that at least 40% of patients treated for depression do not respond to the initial trial of antidepressant drug medication [151], and that at least one half of this percentage do not respond satisfactorily to several further treatment trials [152], SD should be considered among the first-line antidepressant strategies for mood disorders.

In the acute treatment of a major depressive episode, the few trials which compared treatment with antidepres-

sant drugs alone or combined with SD suggested that the main benefit obtained with SD is the hastening of antidepressant response [45, 78, 82]. This effect is obtained by combining SD with drugs soon at the beginning of treatment [45], thus skipping the usual 2 weeks' period of latency of action of antidepressant drugs.

In the long term, treatment of patients affected by bipolar depression with SD and lithium or with antidepressant drugs leads to comparable rates of sustained remission [47, 50], but with the obvious benefit of overcoming the need of unwieldy maintenance treatment with antidepressants, which leads to the dilemma of choosing between a high risk of relapse in the absence of a maintenance treatment with antidepressants [153], and the risk of developing treatment-induced mania, observed in roughly one quarter of bipolar patients receiving combined antidepressant drugs [123].

Conclusions

In recent years, a growing body of literature on the safety and efficacy of SD in everyday psychiatric clinical settings and the biological underpinnings of its action support the inclusion of this technique among the first-line antidepressant strategies for mood-disordered patients [9]. This technique has passed the experimental developmental phase and reached the status of a powerful and affordable clinical intervention for everyday clinical treatment of depressed patients.

Some issues need further research. In particular, the available literature does not allow (1) dose-response relationships among duration, timing and repetition of wake and antidepressant effects to be defined and (2) comparative assessment of the efficacy of the different techniques proposed over the decades (single vs. repeated, total vs. partial SD). Nevertheless, all the proposed techniques share a similar therapeutic status in terms of efficacy and favorable side effect profile, and can thus be freely chosen by the clinical psychiatrists following evaluation of the patient's psychopathological condition and clinical needs.

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