

Sleep Deprivation in Depression: What Do We Know, Where Do We Go?

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Manipulations of the sleep-wake cycle, whether of duration (total or partial sleep deprivation [SD]) or timing (partial SD, phase advance), have profound and rapid effects on depressed mood in 60% of all diagnostic subgroups of affective disorders. Relapse after recovery sleep is less when patients are receiving medication; it may be prevented by co-administration of lithium, pindolol, serotonergic antidepressants, bright light, or a subsequent phase advance procedure. Diurnal and day-to-day mood variability predict both short-term response to SD and long-term response to antidepressant drug treatment. These mood patterns can be understood in terms of a "two-process model of mood regulation" based on the model well established for sleep regulation: the interaction of circadian and homeostatic processes. The therapeutic effect of SD is postulated to be linked to changes in disturbed circadian- and sleep-wake-dependent phase relationships and concomitant increase of slow-wave-sleep pressure; additionally, SD-induced sleepiness may counteract the hyperarousal state in depression. This model has the advantage of providing a comprehensive theoretical framework and stringent protocols ("constant routine," "forced desynchrony") to dissect out specific disturbances. Many aspects tie in with current serotonergic receptor hypotheses of SD action. A treatment inducing euthymia in severely depressed patients within hours is an important therapeutic option that has come of age for clinical use. Biol Psychiatry 1999;46:445-453 © 1999 Society of Biological Psychiatry

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Introduction

Thirty years ago, the first experimental total sleep deprivation (SD) in a depressed patient with severe insomnia revealed an unexpected and paradoxical improvement the following day (Pflug and Tölle 1971). The remarkable transformation of often deeply depressed,

psychotic, suicidal patients in the course of a few hours into their normal pre-morbid "selves" convinced many psychiatrists at that time of the extraordinary importance of this phenomenon. Many studies followed, resulting in widespread consensus that SD can have antidepressant effects. It also turned out that subsequent sleep tends to reverse this improvement. The original interest and investment in clinical research and application faded away.

In our opinion, two factors may be responsible for the current lack of interest. First, considerable relapses were frequently observed after recovery sleep. Second, the dominance of pharmacology and neurochemistry in research on pathogenesis and therapy of psychiatric disorders may be responsible. It is difficult to obtain funding for non-pharmacological and non-neurochemical clinical research (the same is true for another efficacious antidepressant modality, light treatment). Nevertheless, the rapidity and the magnitude of the clinical changes brought about by SD and sleep still remain highly intriguing and may provide clues for understanding the pathophysiology of depression. In fact, it is surprising that no pharmaceutical company has focused on this model in the search for that much-needed rapid-acting antidepressant; don't clinicians want a drug that works within a day?

This review will not be an update of previous summaries (Wu and Bunney 1990; Kuhs and Tölle 1991; Elsenga 1992; Leibenluft and Wehr 1992). It reiterates and extends the issues brought up in recent detailed reviews (Wirz-Justice 1995; Van den Hoofdakker 1997). We wish to reintroduce SD on the clinical and scientific agenda. A renewed attention is justified, not only because of its intrinsic importance, but also because of new developments in the clinical application of SD and in theoretical concepts of the mechanisms underlying the regulation of mood.

Clinical Aspects

For Whom Does Sleep Deprivation Work?

There is an extraordinarily broad response to SD in depression, irrespective of the syndromal classification. Patients with "endogenous" characteristics (even those with severe psychotic features) respond more often than those showing "neurotic" features (75% vs. 48%, Wu

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and Bunney 1990; 68% vs. 33%, Elsenga 1992). There is some empirical evidence that bipolar depressed patients respond more often than recurrent unipolars (Szuba et al 1991; Barbini et al 1998). Although approximately 25% of bipolar patients have been reported to become hypomanic or manic after SD, this response is mainly characteristic of rapid cyclers. A new investigation of a large population ($n = 206$) of bipolar depressed patients revealed a lower rate of ca. 5% switches after SD, not associated with medication status (Colombo et al 1999). Men and women respond equally well. Neither age, number of hospitalizations, earlier treatments, duration of the episode or severity of depression appear consistently related to responsiveness to SD (Kuhs and Tölle 1991; Elsenga 1992). Positive findings have been reported in schizophrenic patients with negative symptoms and with post-psychotic depression, in patients with premenstrual depression, and in depressive pseudodementia. In contrast, SD does not improve anxiety disorders (for references, see Van den Hoofdakker 1997).

What Does the Sleep Deprivation Response Look Like?

Cross-sectional data on many hundreds of depressed patients of all diagnostic subcategories (Wu and Bunney 1990; Wehr 1990; Elsenga 1992) show substantial positive responses the day following a total SD (59%, 60% and 56%, respectively). The time course of a positive response to SD usually begins in the second half of the night. The term "nonresponse" ranges from lack of any change to extremely negative response (Van den Hoofdakker and Beersma 1998).

How Consistent Is the Positive Sleep Deprivation Response?

Lack of antidepressant response to the first SD does not mean that the patient will not respond to further SDs (Pühringer et al 1975; Fähndrich 1988; Gordijn et al 1995). Reanalysis of data from the first two studies (total $n = 80$), where multiple SDs were carried out, revealed that 44% of the patients showed consistent positive responses, and in a further 27% no response to SD was followed by positive responses. In patients with only 2 SDs, a positive response followed by no response or two consecutive SDs without responses, was found in 20% of the cases. The small group who did not respond after 3 or more SDs (9%) could be considered the group of "real" non-responders. Rapid-cyclers show a pattern of increased responsiveness to repeated SDs, suggesting a possible "kindling" effect (Gill et al 1993).

Sleep Deprivation: With or Without Drugs?

In view of its transient and variable effects, SD alone has not been considered an adequate option for clinical use. Therefore it is important to investigate its interactions with antidepressant drugs.

Antidepressant medication has little influence on rates of response to SD (Van den Hoofdakker 1997), but may prevent relapse: drug-free versus medicated 83% versus 59% (Wu and Bunney 1990) and 73% versus 47% (Elsenga 1992). These data concern the responses to 1 single SD and the subsequent recovery night. There is evidence however, that drugs can increase the susceptibility to multiple SDs (Elsenga and Van den Hoofdakker 1990). Addition of drugs can also potentiate the SD effect, as recently exemplified in a placebo-controlled trial of pindolol combined with SD in bipolar depression (Smeraldi et al 1999). This potentiation may be specific to serotonergic drugs: the dopamine agonist amineptine prevented the antidepressant effect of SD (Benedetti et al 1996).

Conversely, multiple SDs might improve response to drugs, as reported in a number of uncontrolled, open studies in "therapy-resistant patients" (Leibenluft and Wehr 1992; Van den Hoofdakker et al 1994; Benedetti et al 1997). This points to a clinically feasible application. Especially important for a longer lasting clinical improvement seems to be the combination of SD with lithium (Baxter et al 1986; Grube and Hartwich 1990; Szuba et al 1994; Gordijn et al 1998), as recently substantiated in an impressive 3-month follow-up study clearly demonstrating sustained response to 3 consecutive SDs only in lithium-treated bipolar patients (Benedetti et al 1999). Further, other serotonin-related treatment strategies have been able to prevent relapse: daily application of bright light after partial SD (Neumeister et al 1996) or tryptophan depletion (Neumeister et al 1998).

What Does the Course of Mood after Recovery Sleep Look Like?

Very little is known about the course of mood after recovery sleep. In most cases an increase in depressive complaints is experienced immediately after sleep termination by both the patient and the environment. Short naps the day after SD are followed by both positive and negative mood responses, with morning naps more detrimental than afternoon naps (Wiegand et al 1993). Even short bouts of microsleep may prevent the full antidepressant effect of partial SD developing (Hemmeter et al 1998).

Although most clinicians and researchers retain the notion that the antidepressant effect of SD is completely lost after 1 night of sleep, the literature contradicts this

assumption, at least in medicated patients: as indicated earlier, relapse rates range between 47%–59%. More importantly, a recent study provides evidence that a beneficial effect on mood is detectable for at least 4 days after SD in lithium-treated patients. The mood level on these days is significantly better than the mood level on 4 consecutive days with normal sleep (Gordijn et al 1998).

Predictors of Sleep Deprivation Response

Studies on the possible psychobiological predictors of the SD response have yielded disparate and inconsistent results (for reviews see Kuhs and Tölle 1991; Van den Hoofdakker 1994; Kasper and Möller 1996). The only exception concerns the relationship between SD response and pre-SD levels of “arousal” or “activation.” High vigilance levels, high behavioral activation and low levels of tiredness are related to a favorable SD response (Bouhuys et al 1989, 1995; Szuba et al 1991). Levels of transmitter metabolites in urine and cerebrospinal fluid indicate that low peripheral sympathetic activity and high central noradrenergic activity favor response to SD (Kuhs and Tölle 1991; Kasper and Möller 1996).

In accordance with these results, PET and SPECT studies have suggested that patients with high metabolic rates in limbic areas are likely to respond to SD, and later, to antidepressant medication (Ebert et al 1991; Wu et al 1992). A new study extends this finding to a larger group of patients: at baseline, high metabolism in the ventral anterior cingulate was found in those who responded to SD, followed by decreased metabolism in the medial prefrontal cortex after clinical improvement (Wu et al 1999). There may be a correlate in the findings of some authors that higher thyroid function predicts positive response to SD (e.g., Baumgartner et al 1990; reviewed in Kuhs and Tölle 1991).

Diurnal Variation of Mood Revisited

Cross-sectional studies show that diurnal variation of mood (DV) appears to be a predictive patient characteristic. Patients with positive DV (better in the evening) on the day before SD tend to respond more favorably than those with negative DV (worse in the evening) or no DV (Reinink et al 1990; Haug 1992).

In a prospective longitudinal study it was investigated whether within patients the response to SD could be predicted from the mood pattern on the day prior to SD. It turned out that within an individual it was not the (positive or negative) DV pattern on the day prior to SD that correlated positively with SD response, but the amount and magnitude of DVs during the depressive episode (Reinink et al 1993). More detailed analyses showed that the variability of mood fluctuations is an even better

predictor of SD response: the larger the variability of daily and day-to-day mood fluctuations the more favorable the response to SD (Gordijn et al 1994; 1995). Of clinical relevance is that both this mood variability, and a beneficial effect of SD, predicted a high chance for a favourable outcome after 6 weeks of antidepressant drug treatment (Gordijn et al 1998). This is in accordance with the findings in a large antidepressant treatment study ($n = 116$): patients with greater DV amplitude (higher day-to-day “rhythmic activity” over 3 weeks) were those who preferentially responded (Haug and Stieglitz 1990).

Mechanisms Underlying the Effects of Sleep Deprivation

The central characteristic of the mood disorders is by definition the disturbance of one of the most complex and fundamental processes regulating our interaction with the environment: the regulation of mood. SD is a complex intervention with impact on a host of levels of functioning, covering the entire area from social interactions to molecular processes. Thus, the mechanisms explaining SD response can be looked for on many levels.

Let us begin by narrowing these down. Psychological mechanisms are unlikely to provide a complete explanation, because the acute improvement after SD is unprecedented in the psychotherapeutic literature on the category of severely ill patients susceptible to SD (reviewed in Van den Hoofdakker 1997). Positive expectations are counterintuitive for depressed patients who perceive sleep loss as a central problem; further, why would recovery sleep threaten mental well-being? SD involves the manipulation of many potentially important nonpsychological variables. Where these have been tested (e.g., body posture, motor activity, environmental light intensity), they do not appear determinant of the antidepressant response (Van den Hoofdakker 1997).

There is obvious personal bias in the choice of disciplines to study biological mechanisms in psychiatry. Pharmacology and neurochemistry dominate. This is understandable in view of the central role that was played by antidepressant drugs in the development of biological theories. The acute and transient therapeutic response to SD must be mediated by mechanisms different from those mediating the gradual improvement obtained with antidepressants.

In the area of neurochemistry there are many potentially promising studies, though they will not be reviewed here in detail. In particular, serotonin is a major neurotransmitter candidate, being involved in both sleep and circadian rhythm regulation, and the modulation of mood state in humans. There is indeed a growing body of evidence that serotonergic (5HT) mechanisms, in

particular, down-regulation of presynaptic 5HT_{1A} receptors, may be involved in the antidepressant action of SD (e.g., Prévot et al 1996). Clinical trials using 5HT-related treatment modalities have revealed interactions with SD to potentiate response or prevent relapse—lithium, clomipramine, fluoxetine, the 5HT_{1A} receptor antagonist pindolol, bright light or tryptophan depletion (see “Sleep Deprivation: With or Without Drugs?”). An important clue comes from the finding that a functional polymorphism within the promoter of the 5HT transporter gene, associated with a better response to fluvoxamine and paroxetine (Smeraldi et al 1999; Zanardi et al 1999), is also associated with better mood amelioration after SD (Benedetti et al 1999). It is also possible that altered serotonergic function in depression is merely a reflection of another more primary pathogenetic process, such as hypercortisolemia or immune dysfunction (SD alters immune response e.g., Dinges et al 1995).

A new psychostimulant theory implicating dopaminergic mechanisms in the antidepressant effect of SD (Ebert and Berger 1998) requires future studies to test this intriguing hypothesis. That a dopamine reuptake inhibitor prevents the antidepressant effect of repeated SD is a surprising negative finding (Benedetti et al 1996). Still at the experimental level is the quest for specific genes that are expressed after sleep deprivation (e.g., Borbély and Tononi 1998).

Since extensive developments in understanding the regulation and dysregulation of mood have recently taken place in the field of sleep physiology and chronobiology, we have chosen to dedicate this review to these functional interactions, embedding the discussion within the explanatory framework of the two-process model of sleep regulation.

Models of Sleep Regulation

The two process model of sleep regulation postulates interaction of a homeostatic process S and a circadian process C (Daan et al 1984). Sleep need is represented by process S and is reflected in EEG slow wave activity (SWA), i.e., power density in the frequency range below 4Hz. The level of sleep need depends on the duration of prior wakefulness and sleep: it increases exponentially with increasing duration of wakefulness and decreases during non-rapid-eye-movement (NREM) sleep. Sleep onset and sleep termination are determined by the level of S and by a gating system consisting of two thresholds under control of the circadian process C. Thus, apart from conscious decisions elicited by external social or psychological factors, sleep need and the circadian pacemaker dictate the timing of (NREM) sleep. The regulation of REM-sleep is complicated: in addition to a homeostatic

component, REM-sleep propensity and timing appear to be governed by an interaction between circadian and ultradian mechanisms, controlling the distribution over 24 hours, as well as reciprocal interaction of NREM- with REM-sleep.

The amplitude and phase characteristics of process C can be estimated in rhythms (such as core body temperature or melatonin) measured under the controlled conditions of a “constant routine” protocol (subjects kept in bed, supine posture, regular small isocaloric snacks, with low light intensity and constant temperature). The disadvantage of the classic 40-hour constant routine is the sleep deprivation thereby induced over time. To avoid this problem, a second method has been developed, the “forced desynchrony” protocol. When subjects are forced for many days to be awake and sleep on an artificial daylength schedule outside the range of entrainment of the human circadian system (<22 hours or >28 hours), the sleep-wake cycle follows the imposed daylength but circadian rhythms do not. This desynchronization permits separation of the respective contribution of the two processes C and S to the regulation of overt rhythms (Dijk et al 1992; Hiddinga et al 1997). Such experiments have demonstrated that interactions between the circadian system and the sleep-wake cycle determine the course of many variables, such as sleepiness, alertness, cognitive performance and, last but not least, mood (Dijk et al 1992; Boivin et al 1996; Van den Hoofdakker 1997).

Models of the Effects of Sleep Deprivation in Depression

Internal Coincidence

The “internal coincidence hypothesis” (Wehr and Wirz-Justice 1981), an extension of the phase advance hypothesis for depression (Wehr et al 1979), assumes that the phase-angle between an advanced circadian pacemaker and the sleep-wake cycle is depressogenic. Depressive patients sleep at the wrong biological clock-time, like shift workers or transmeridian travellers. The second assumption is that SD is effective because the coincidence of sleep with the critical phase is avoided. Recovery sleep restores this coincidence.

S-Deficiency

The S-deficiency model proposes a deficient build-up of process S (i.e., sleep need) in depression, with process C remaining unaffected (Borbély and Wirz-Justice 1982). SD is assumed to be therapeutic because the level of S is transiently increased to normal; relapse occurs after recovery sleep due to the return to low levels of S.

REM-Sleep

A cluster of related hypotheses suggests that abnormalities in the ultradian rhythm of REM-sleep play a dominant role in depressed patients. These models assume disturbed neurochemical interaction mechanisms. Since selective REM-SD is not only a heroic task but requires weeks to elicit an antidepressant effect (Vogel et al 1980), it can hardly be responsible for the clinical effects of a single night's SD.

Slow-Wave-Sleep Suppression

REM-sleep deprivation experiments in healthy subjects have led to gradual suppression of SWA (Beersma et al 1990; Brunner et al 1990). Total SD is obviously accompanied by acute suppression of SWA. Since REM-SD in depressives leads to gradual improvement (Vogel et al 1980) and total SD to acute improvement, it has been postulated that the suppression of SWA is causal to the antidepressant effects of both REM-SD and total SD (Beersma and Van den Hoofdakker 1992).

Arousal, Cerebral Fatigue

Obviously, sleep subserves restorative brain processes and sleep loss, particularly loss of NREM-sleep, causes "fatigue of the brain" (Horne 1991). One of the paradoxical consequences of sleep loss in depressed patients is the increase of subjective tiredness and sleepiness combined with improvement of energy and mood (Van den Burg et al 1992). According to these authors, SD-induced cerebral fatigue might break the distressing state of hyperarousal depressives can be in, resulting in simultaneous feelings of relief and tiredness.

Manipulations of the Sleep-Wake Cycle Other Than Total Sleep Deprivation: Duration or Timing?

The models presented essentially postulate two factors that may be responsible for changes in depressive state after SD and recovery sleep: manipulations of sleep duration (and therefore of the level of process S) or manipulation of sleep timing (and therefore the interaction between processes S and C). Which is crucial?

For this question, partial SD has served as a theoretical tool. The antidepressant effects appear equivalent to those of total SD (reviewed in Van den Hoofdakker 1997). Although clinicians routinely restrict sleep to the first half of the night, unequivocal superiority of this strategy to restricting sleep to the second half of the night has not been shown (Giedke et al 1992). Thus, simply a limited duration of sleep (and thus the level of process S) may be essential, rather than the timing.

A second approach has been to shift sleep, not curtail it. A 6-hour advance of sleep timing induced positive, long-lasting responses in a number of uncontrolled studies (reviewed in Van den Hoofdakker 1997) indicating that the timing of sleep, and thus the phase relationship between sleep and the circadian system, might indeed be a crucial element in the mood changes that take place during or after sleep-wake manipulations. In other words the timing of sleep would be crucial. The possibility is not excluded that with shifting sleep the duration of sleep is also changed and, therefore, process S.

The above approaches have also been used to attempt to preserve the SD-induced improvement. First, after antidepressant response to total SD, partial SD was carried out in the recovery night. Relapse was not prevented, neither when sleep was restricted to the early part of the night, nor to the later part (Elsenga et al 1990). Relapse was prevented when a total SD was followed by an acute 6-hour phase advance of sleep, day by day slowly reverting sleep timing back to normal (Berger et al 1997). Two further studies have demonstrated maintenance of the clinical response to SD, with advanced sleep phase (17-24 hours) better than a normal (23-06 hours) or delayed sleep period (02-09 hours) (Riemann et al 1996, 1999).

Mood Regulation

Since mood is such a complex phenomenon, modulated moment to moment by myriad factors within and without (from hormones to social situations), insight into its regulation is difficult. Yet surprisingly, mood, as sleep, follows similar laws of nature. Self-rated mood undergoes a clear circadian rhythm, that can be revealed in a constant routine protocol (e.g., Wirz-Justice 1995). Mood is also dependent on a homeostatic component. The exponential increase of sleep need during wakefulness has a parallel in a decrease in alertness and mood (Boivin et al 1996; Van den Hoofdakker 1997). For alertness, it has been shown that the circadian system counteracts the homeostatic changes: under normal synchronous conditions the phase of the circadian modulation of alertness is such that the peaks and troughs coincide with the sleep-wake dependent troughs and peaks, maintaining vigilance till the end of the day (Dijk et al 1992). Probably the same mechanisms can be proposed to maintain constant levels of mood during normal days (Boivin et al 1996).

Diurnal mood variations and depressed mood might arise from changing interactions of the two processes S and C. Two experiments can be adduced to provide evidence for this hypothesis. In 11 healthy young men undergoing a "short" 20 hour forced desynchrony protocol (Figure 1), mood ratings showed changing DV patterns and amplitude day by day. These raw data represent a

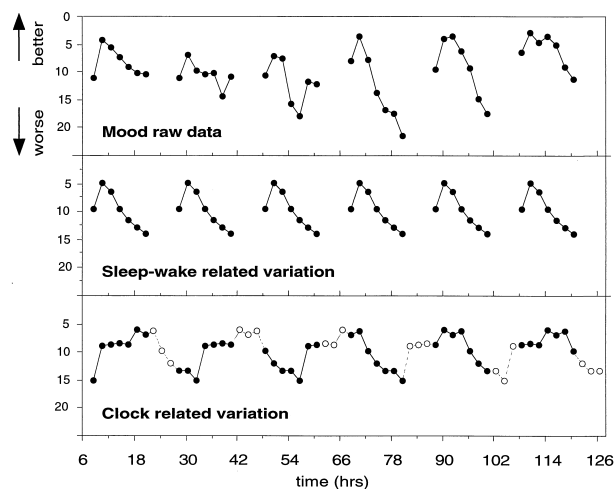


Figure 1. *Upper panel*: Average time course of 2-hourly self-ratings of mood during wake (using an adjective mood scale) in 11 healthy subjects living on six 20-hour “days” while in a time-isolation unit. This “forced desynchrony” protocol permits analysis of the raw data in terms of the sleep-wake dependent variation of mood after correction for the circadian modulation (*middle panel*), and the circadian modulation of mood after correction for the sleep-wake dependent variation (*lower panel*) (see text for details). Redrawn from Van den Hoofdakker et al 1997.

mixture of circadian and sleep-wake components. The forced desynchrony protocol permits identification of the “pure” circadian contribution and the “pure” sleep-wake-related contribution and dissects such mood curves as cleanly as physiological variables (Hiddinga et al 1997). The middle panel shows the influence of the sleep-wake cycle without circadian influence: after a short improvement in the first hour of wakefulness, mood deteriorates in an exponential fashion. The lower panel shows a circadian rhythm of mood state independent of time awake. The different patterns of mood in the upper panel thus can be largely explained by the changing phase-relationships between the sleep-wake cycle and the circadian system induced by a forced desynchrony.

To quote Van den Hoofdakker (1997) “These findings may shed some light on the mechanisms underlying the spontaneous instability of mood in depression, and its close relationship with susceptibility to improve after SD. The coincidence of particular levels of sleep need and particular circadian phases might be the unifying explanation of the diurnal and day-to-day variability of mood as well as the variability of the effects of curtailment of sleep and recovery sleep. The latter would prevent, respectively restore such coincidence.”

Preliminary evidence supporting this explanation comes from the very first sleep phase-advance experiment in a depressed patient (Wehr et al 1979). DV patterns changed

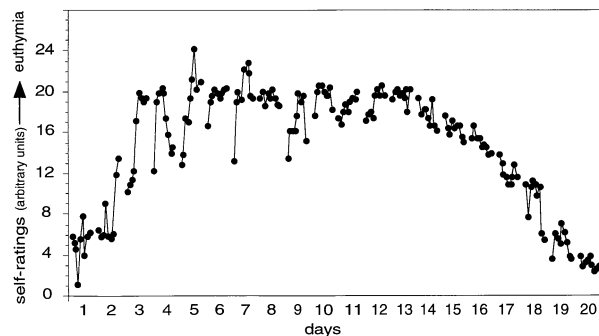


Figure 2. Time courses of 2-hourly self-ratings of mood during wake in a depressed patient (Bipolar II, f, 57y) over 20 consecutive days following a 6 hour phase advance of her sleep-wake cycle (sleep from 5 p.m. to 1 a.m.). Unpublished data, Wehr and Wirz-Justice; experimental details in Wehr et al 1979.

amplitude and level day by day for 3 weeks after a 6 hour phase-advance of the sleep-wake cycle (Figure 2). This is not a forced desynchrony protocol, so the sleep-wake-related and circadian clock-related components cannot be separated out. Yet, if one compares these day-to-day diurnal variations of mood, induced by a 6 hour phase-advance of the sleep-wake cycle in a depressive patient, with the day-to-day mood ratings, induced by a forced 20 hour sleep-wake cycle in healthy subjects, there are some remarkable similarities. One gets the impression that also in the patient, a circadian rhythm of mood appears to move through the window of time awake. In other words, mood swings appear to be grounded in the interaction of these two physiological processes. We now have sophisticated protocols to test this hypothesis and an elegant model within which framework the findings can be interpreted.

Dysregulation of Mood in Depression

As shown in the former paragraph, the instability of mood can be explained by an instability of phase relationships between the need for sleep (process S) and processes controlled by the circadian system. In healthy subjects, some phase relationships are favorable, others unfavorable, and this may also be the case in depressed patients. Sleep deprivation may produce its antidepressant effects by increasing sleep need and thus changing the phase relationship between sleep need and processes under circadian control. The explanatory power of this “two-process model of mood regulation” is limited to these aspects. The model does not explain why patients are depressed, that is, why mood has deteriorated to a pathological degree. It also does not account for the fact that SD may even normalize mood. The arousal and cerebral fatigue hypothesis may offer more appropriate explana-

tions. The depressive mood would be due to pathological levels of arousal, and SD would break this aroused state. Further, none of these are incompatible with a serotonergic hypothesis of depressed mood, since it is long known that neurotransmitter functions undergo a dynamic change over the circadian cycle, at every level from synthesis to receptor sensitivity (e.g., Wirz-Justice 1987).

Back to the Clinic

Given that in healthy subjects each moment's mood is physiologically based on the interaction of time of day and elapsed time awake, it is evident that mood can be influenced in many ways. It can vary from day to day because of a good night's sleep or a bad one, because of a nap, different times of outdoor light exposure, the use of drugs, etc., not to mention psychological events. This complexity is daunting, but the very fact that something so subjective as mood can be reliably measured and predictably modulated provides a challenge for developing clinical applications.

Let us attempt to outline a pragmatic scheme for treating depression using the above concepts and the available empirical data. First, we may attempt to increase the level of Process S or SWA pressure by changing the duration and timing of sleep. Second, the amplitude and phase of Process C could be modified with appropriately timed bright light, ensuring stable entrainment. Once the patient is improved, the problem is to maintain this improvement. Empirical data suggest that this may be achieved by light therapy, lithium, pindolol, and preferentially serotonergic antidepressants; and non-pharmacologically, with a phase advance of the sleep-wake cycle.

SD response is most marked in those individuals manifesting daily and day-to-day variability in mood. These individuals also respond best to antidepressant treatment (Haug and Stieglitz 1990; Gordijn et al 1998). Thus, the very instability of depressive state predicts SD-induced short-term and drug-induced long-term amelioration. In clinical practice, this means one should look out for this mood lability: does it also mean, one should induce it? Perhaps the simple procedure of rating mood two to three times a day for a week could provide an empirical basis for selecting those depressed patients "ready" to improve. A corollary of this hypothesis, is that we should induce day-to-day variability in mood in depressed patients before treating them. Primitively put, rattle the system; chronobiologically expressed, realign unfavorable phase-relationships.

Can we link these concepts to classical drug trials in depression? A recent metaanalysis of the placebo run-in period revealed that *any* mood change during this baseline period was a predictor for more favorable prognosis 6

weeks later—whether or not assigned to drug or placebo (Quitkin et al 1998). This is an important finding now repeated in two further analyses (Quitkin, p.c.). A small improvement during 10 days placebo pill treatment appeared to identify patients with an increased likelihood of going into remission. We posit that these individuals showed day-to-day variability.

In summary, this review was written to rekindle interest in scientific and clinical studies of SD. It is our opinion that manipulations of sleep may contribute to our understanding of the pathogenesis of depression, and furthermore, enlarge the therapeutic armamentarium with rapid and efficacious treatment modalities.

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