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State-of-the-Art Review

Sleep Research in Affective Illness: State of the Art Circa 1987

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Sleep research in affective illness has advanced considerably during the last 10 years, as evidenced in publications from both North America and Europe. In this review we highlight several facets of these research endeavors, including conceptual and methodologic advances. We also review the now-impressive body of objective data on sleep changes associated with affective illnesses, emphasizing several issues that were considered controversial and unresolved as recently as 5 years ago, such as the distribution of REM latency and the quantification and temporal distribution of NREM slow wave activity. Progress in the developmental aspects of sleep in depression has also taken place, particularly in regard to childhood forms of depression and late-life depression. Additional information has been developed concerning the specificity of these changes in depression versus other psychiatric disorders such as schizophrenia and dementia of the Alzheimer type. Other recent studies have dealt with how best to define REM latency in depression, the clinical and polysomnographic correlates of sleep onset REM periods (SOREMPs) in depressive illness, and studies of REM latency variability in depression (particularly the clinical implications of such variability).

While considerable progress has thus been made in further defining and quantifying the descriptive features of sleep during acute episodes of affective illness, additional information has also been published regarding the effects on sleep of a variety of acute antidepressant treatments, including tricyclic antidepressants, REM sleep deprivation, and total sleep deprivation. Recent information concerning longitudinal changes of sleep in depression, particularly in relation to clinical remission, has also been published. Thus, a more consistent body of information is emerging in the state- versus trait-like nature of sleep changes in depression.

Finally, progress in sleep research in affective illness has not been limited to a broadening of the empirical database, though the latter has been considerable. Much prog-

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ress on conceptual and methodological fronts has also taken place, leading to the development of testable hypotheses in the sleep physiology of depression and to new interpretations of old findings. This progress has been evidenced by the publication of several different models on the pathophysiology of depression using electroencephalographic (EEG) sleep measures. Such models, which have also attempted to account for the growing body of neurochemical, biological rhythms, and ontogenetic sleep data, are already determining current directions of research in this area and are likely to bear upon the direction of investigation during the next decade. Sleep research in depression is broadening its previously descriptive emphasis on baseline or unchallenged sleep to include the use of naturalistic and pharmacologic probes for testing predictions derived from different models. Sleep measures are also being increasingly integrated with other types of psychobiological measures obtained concurrently in the same patient, such as measures of psychomotor activity, neuroendocrine activity, and circadian rhythms of temperature, mood, and cognitive performance. In essence, we are witnessing broad and multifaceted progress in both empirical and conceptual areas of psychiatric sleep research in affective illness.

CONCEPTUAL ADVANCES

Major depression is a syndromal diagnosis, and several clinically distinct subtypes exist within this diagnostic grouping, e.g., bipolar, delusional, and endogenous-melancholic forms. However, it is also likely that further biological heterogeneity exists within clinically distinct subgroups, both at the level of pathophysiology and at the level of treatment response (e.g., 1). To date, studies of sleep alterations have often focused on more severely ill samples with endogenous or melancholic depressions. Thus, such studies have left partly unresolved whether abnormalities seen validate our clinical subtypes [as suggested by Rush et al. (2)] or represent in some fashion a continuum of severity.

Relative to theory development, most sleep research on affective illness, especially unipolar subtypes, has focused on the pathophysiology that is concurrent with, or underlying, acute clinical signs and symptoms. To build a comprehensive etiological model, however, it is necessary to develop lines of evidence bearing more directly on factors indexing vulnerability to affective illness. Identification of sleep physiological abnormalities that precede clinical episodes of major depression, especially the first episode, warrants stronger inferences with regard to the potential etiologic role of these abnormalities. In other words, identification of a sleep abnormality does not necessarily imply etiopathogenetic significance. Conceivably, a given disturbance of sleep may be present only during the episode of depression (state marker), may antedate the clinical episode (trait marker), or may persist during clinical recovery (i.e., be a marker of a past episode or a trait marker).

Viewed from this perspective, one can formulate an interesting question and a testable hypothesis about such sleep abnormalities of depression as shortened REM sleep latency. For example, is it possible to use shortened REM sleep latency as an independent variable to predict the likelihood of either a past history of affective disorder or the future development of affective disorder? The hypothesis suggested by such a question is that it is possible to predict the past or future occurrence of depression in a high-risk group if one knows the REM latency. Research to test this hypothesis is now being conducted by Giles and colleagues in Texas and Pennsylvania.

It is now known that REM latency and other EEG sleep measures show little change over time in inpatients receiving placebo (3). These studies have high test-retest reliability over at least 2- to 6-week intervals. Moreover, the findings of Hauri (4), Schulz et al. (5), Cartwright (6), and Rush et al. (7) suggest that chronic sleep abnormalities, including reduced REM latency, persist beyond the clinically symptomatic period. Thus, because it appears that REM latency is reduced and stable in depression, the question arises as to whether this parameter is an indicator of continued vulnerability to depression, a consequence of depression that remits more slowly than the clinical episodes, or a potential predictor of depression in people who are unaffected but at risk. To answer this question, a number of investigators (e.g., Rush, Giles, Roffwarg, and Kupfer) are shifting to longitudinal follow-up studies with repeated sleep measures during, after, and just before recurrent episodes of depression.

In this same context, longitudinal evaluation of change in clinical and sleep data may shed some light on neurobiological and psychobiological mechanisms of response to treatment. Most effective somatic treatments are known to produce alterations in REM sleep, and, with respect to tricyclic antidepressant therapy, acute suppression of REM sleep measures appears to be significantly correlated with both clinical response and plasma tricyclic levels (e.g., 8–10). Vogel et al. (11) have proposed that REM sleep suppression is the key mechanism underlying treatment response (i.e., antidepressants work precisely because they are REM sleep suppressants), a suggestion based not only on the REM sleep-suppressant effects of efficacious antidepressant drugs, but also on the antidepressive effectiveness of REM sleep deprivation itself in endogenously ill patients (REM sleep disinhibition paradigm). Vogel et al. (11) have also reported that the extent of late REM sleep rebound following REM sleep deprivation is significantly correlated with final clinical response. This heroic and important work awaits replication.

A related conceptual issue is whether sleep abnormalities in affective illness are primary or secondary changes. That is, do sleep changes represent epiphenomena, or do they reflect the basic biological changes associated with, and responsible for, the presence of an affective illness and its responsiveness to treatment? The fact that sleep deprivation and REM deprivation have well-known antidepressant effects suggests that there must be links between the regulation of sleep and the regulation of mood in affective illnesses. (Similarly, the fact that each intervention has its own distinctive time course of antidepressive efficacy may suggest that each works through different neurobiological mechanisms or alternatively that one is more powerful than the other.) Another example is that sleep changes may affect other biological rhythms, leading to abnormalities in the neuroendocrine secretory access. For example, since the sleep-wake cycle itself affects the turning off of cortisol and the turning on of prolactin secretion, as well as growth hormone, it would appear that sleep abnormalities may affect various neuroendocrine rhythms. These in turn could be related to the onset and intensity of the affective illness. Further, the apparent persistence of sleep abnormalities into remission and their correlation with treatment response suggest that these abnormalities are not epiphenomenal but have, instead, a direct relation to etiopathogenesis and the neuropsychobiology of treatment response.

These conceptual issues are further exemplified by a recent study of sleep in delusional depressives (12). Comparison of pretreatment EEG sleep measures in delusional and nondelusional depressives indicated that the delusionals had significantly decreased generation of REM sleep and REM activity (~20% less than nondelusionals)

but higher frequency of SOREMPs (50 vs. 30%) than did nondelusional depressives, even after controlling for effects of age, severity, and agitation. Diminished generation of REM sleep in delusional depressives might implicate functional hyperactivity of central dopaminergic systems, since administration of dopaminergic agonists to healthy controls results in increased arousal and suppression of REM sleep time and percentage (13). Further, the efficacy of adjunctive treatment with dopamine blocking neuroleptics in delusional depression also suggests a possible dopaminergic abnormality in the disorder. As will be reviewed below, available data suggest that the sleep abnormalities of depression may result from perturbations in several neurotransmitter systems.

METHODOLOGIC ADVANCES (TABLE 1)

Progress in sleep research in affective illness has been facilitated by increasing sensitivity to sources of unwanted variance, both patient and investigator related. Psychiatric sleep research in the late 1970s and 1980s has been assisted by developments of increased diagnostic precision, such as research diagnostic criteria (14), which reflect better operationalized diagnoses, particularly of affective disorder subtypes. This development has made it somewhat easier to select homogeneous groups of patients for sleep research studies. Some investigators are also using biological measures like REM latency to further define subgroups for study. For example, Giles et al. (15) have reported that reduced REM latency is related to endogenous depressive symptoms of terminal insomnia, pervasive anhedonia, unreactive mood, and appetite loss.

Second, the importance of ruling out concurrent medical or neurological syndromes before the sleep investigation of major depression has generally been recognized. Indeed, several investigators have reported differences in the sleep of patients with primary depression versus depression associated with medical disease (e.g., 16,17). In the latter, rate of production of REMs is typically severely diminished.

Third, while it is now generally agreed that baseline or pretreatment studies should be conducted after withdrawal of psychotropic medication, an accepted compromise position has been the use of a 2-week drug-free period. In this same context, recent proposals to use cognitive-behavioral therapy in the treatment of depression seem particularly promising with respect to enhanced understanding of what types of biological dysfunction generally and sleep abnormalities in particular persist in clinically recovering outpatients not exposed to antidepressant drugs. From the viewpoint of sleep research, the major advantage conferred by this strategy is to permit the examination of the stability, or the liability, of sleep variables before, during, and after depression,

TABLE 1. *Methodologic advances in psychiatric sleep research*

Increased diagnostic precision
Improved understanding of investigator- and patient-related variance
Use of biologic criteria for sample definition
Recognition of need to distinguish primary depressive from medical depressive syndromes
Two-week drug-free observation periods
Use of nonpharmacologic treatment strategies (e.g., cognitive-behavioral therapy) to distinguish state- from trait-like alterations
Recognition of need to distinguish entrained from free-running condition
Recognition of need to control interactions among tests
Use of computer for quantification of sleep
Longitudinal follow-up studies
Family psychobiologic studies

solely as a function of clinical state change, without the potentially confounding effects of a somatic intervention.

Fourth, recent studies have dealt with the issue of entrainment and novelty in a more sophisticated manner. Many studies have actually been conducted in the hospital room where patients have resided for several weeks before the investigation and with strict attention to clock time. These procedures have led to a considerable degree of entrainment; thus, issues raised in the early 1970s on adaptation and the stress of the first period of studies have been resolved to some extent. Nevertheless, even though adaptation has been made easier, because current approaches often include simultaneous measurement of several variables (such as the conduct of sleep, neuroendocrine, temperature, and biochemical studies), investigators have had to remain sensitive to the burden of intensive experimental manipulation and to interactions among tests.

Finally, increasing reliance on the computer for quantifying phasic phenomena, such as the temporal distribution and integrated amplitude of REMs and EEG slow wave activity, has led to much finer-grained descriptions of sleep pathophysiology. This in turn has made possible more sophisticated hypothesis generation and testing concerning hierarchical regulation and dysregulation and age-disease interactions.

PROGRESS REPORT OF WORK SINCE THE LATE 1970s

In the following sections, we review progress in the description and quantification of EEG sleep changes in depression and the specificity of such changes to depression. We also detail advances in our understanding of REM latency variability in depression and of interactions between aging and depression in the expression of sleep physiological abnormalities. After a review of EEG sleep alterations during acute antidepressant therapy, we turn to currently available paradigms of sleep and mood regulation in affective illness.

Description and quantification of EEG sleep changes in depression

A constellation of findings characterizes the sleep of depressive patients during acute illness (2,11,18–22). Approximately 90% of depressed inpatients show some form of EEG-verified sleep disturbance. The most predictable sleep abnormalities of endogenous depression include (a) sleep continuity disturbances (i.e., prolonged sleep latency, multiple nocturnal awakenings, and early morning awakening); (b) diminished slow wave sleep (Stages 3 and 4), with a shift of slow wave activity from the first to the second NREM sleep period; (c) an abbreviated first NREM sleep period leading to earlier appearance of the first REM sleep period (earlier, that is, with respect to sleep onset, but not with respect to clock time itself in the entrained condition); and (d) altered intranight temporal distribution of REM sleep, with increased REM sleep time and REMs earlier in the first half of the night. All of these features tend to become more marked with advancing age and thus parallel the normal ontogeny of sleep structure (23,24).

A minority of patients with major depressive disorders, perhaps 10–15%, demonstrate high sleep efficiencies and report spending more time in bed. This finding is often associated with complaints of anergia and psychomotor slowing (25).

While it has been known for many years that depressed patients show a reduction in slow wave sleep (manifested by reduced minutes and percentage of Stage 3 and 4 sleep), the application of the computer for the quantification of slow wave sleep has now shed light on the specific nature of slow wave sleep abnormalities in depression.

Thus, in young adult and middle-aged depressives, reduction both in the absolute number of EEG delta waves during NREM sleep and in the rate of production of such delta activity, that is, a decrease in the number of slow waves per each minute of NREM sleep, takes place (26). Although such reductions characterize all NREM periods, they are most marked in the first NREM sleep period. While nondepressed healthy controls show a linear decrease in the rate of production of slow wave activity across consecutive NREM sleep periods, with highest rates in the first NREM period, by contrast, an altered temporal distribution of slow wave activity is evident in NREM sleep of major depressives. The depressed patients show a reduction in delta activity particularly during the first NREM sleep period compared with the second (26,27). Such an alteration in the number and density of EEG slow waves has also recently been demonstrated in elderly nondemented depressives (27). This finding of weakened slow wave activity, particularly in the first NREM period, is extremely interesting, since it is the length of the first NREM period that also defines the shortened REM latency in the majority of patients with depressive illnesses, especially the endogenous forms (2). This redistribution of slow wave activity from the first to the second NREM period, as well as the increased rate of production of REMs in the first REM period, are relatively more specific to endogenous depression compared, for example, with Alzheimer's dementia (28) and schizophrenia (29).

The abbreviation of the first NREM sleep period in depressive illnesses (or shortening of REM sleep latency, as it usually referred to) remains a robust and widely replicated finding. However, one of the controversies that has beset psychiatric sleep research is whether REM latency in depression has a bimodal or normal distribution (for review, see ref. 30). We believe that this issue has been resolved, and that the resolution has derived from an improved understanding of the sources of variance in REM latency in depression. Specifically, the distribution of REM latency is determined by several independent but probably interactive factors, including the age range of the sample studied, the severity of the depressive symptoms, and finally the subtype of depressive illness. Thus, very abbreviated REM sleep latencies (i.e., <20 min) have been found in association with delusional depression (12,31), but also in association with elderly nondelusional depression (28). If one's sample is heavily loaded with delusional depressives and/or with elderly depressives (i.e., those aged 60 or above), a relatively higher proportion of the REM latency values will be shifted leftward in the overall distribution. By contrast, if one is studying a group of middle-aged depressives without delusional features, the REM latency distribution will be normal, with a mean value of some 30 or 40 min below that of healthy controls. In other words, when age and psychosis are controlled, the apparently bimodal distribution of REM latency in major depression may be replaced by a more continuous unimodal distribution, ranging from 0 to 65 or 70 min (30).

Another robust and relatively specific feature of the sleep of acutely ill depressed patients is the shift of REM sleep into the first REM period (11). In both middle-aged and elderly depressed patients, the length of the first REM period is consistently longer than that of age-matched healthy controls. While the same may also be true of young adult depressed patients, the leftward shift of REM sleep into the first REM period is not as pronounced, suggesting that this shift may reflect, at least in part, an age-mediated disinhibition of REM sleep in depressive illness (11). As well, the density of REMs in the first REM period appears to be greater in middle-aged and elderly depressives than it is in young adult depressives.

The combination of a shortened first NREM period and a lengthened first REM period in depressive patients suggests that the key to understanding the sleep abnormalities in depressive illness could be sought by a more intensive examination of the first 100 min of sleep, that is, the first NREM-REM sleep cycle. Data now emerging from computer-assisted quantification of the first NREM-REM cycle strongly suggest both a diminution in slow wave activity (rate of production) during the first NREM period and a concomitant increase in the rate of production of REMs during the first REM period. This constellation of changes is a key feature of the sleep of depression and will have to be accounted for by any model of sleep-wake dysregulation in depression. As an example of the import of the first NREM-REM sleep cycle to models of depressive pathophysiology, Wehr and Goodwin (32) suggested that the short REM latency of depression might reflect either the earlier occurrence of the first REM period (i.e., a phase advance of the first REM period) or alternatively difficulty initiating sleep with a consequent prolongation of sleep latency and thus shortening of the first NREM period. This issue has been examined empirically in a group of 50 major depressive patients entrained to a regular schedule, 25 inpatients and 25 outpatients (33). In entrained inpatients and outpatients, the clock time of the first REM period was not significantly earlier than that of age- and sex-matched healthy controls; rather, the shortened first NREM period of the depressives was associated with the later retiring time of the depressives and a longer sleep latency. This finding is evidence against a phase-advance hypothesis of REM sleep in depression, but does support the concept of a more specific weakening in the NREM sleep system, as suggested by the two-process model of sleep, to be reviewed below (34). In any case, this remains a controversial area that will continue to receive much attention in the next decade.

Specificity of EEG sleep changes in depression

Impaired sleep continuity and loss of slow wave sleep are common to many psychiatric disorders, including generalized anxiety disorders (35), obsessive-compulsive disorder (36), affective disorders, schizophrenia (37–39), and alcoholism (40). The most extensive laboratory investigations have been carried out in patients with affective disorders and schizophrenia (for review, see ref. 29). There is still controversy concerning the extent to which affective disorders and schizophrenia have different sleep physiological abnormalities. As previously discussed, particularly in endogenous depressions, an abbreviated first NREM sleep period and a prolonged first REM period with heightened rate of production of REMs are very characteristic. Moreover, following REM sleep deprivation, patients with endogenous depression typically demonstrate large increases in early REM sleep above baseline conditions (11). The situation is less clear with respect to schizophrenic patients. Some investigators have reported short REM latency in patients with schizophrenia (e.g., ref. 39), while others have not (for review, see ref. 29). To our knowledge, however, no published investigations have reported the constellation of short REM latency and prolonged first REM period in schizophrenic patients, a constellation that is highly characteristic of endogenous depression. Moreover, patients with schizophrenia who are REM sleep deprived do not show the predictable REM sleep rebound or compensation, particularly early in the night, that seems to be characteristic of endogenous depressives (37).

Extensive sleep physiological studies have also been carried out in patients with probable dementia of the Alzheimer type. The degree of sleep disturbance gradually worsens with progression of the dementia, until there is a loss of sleep-wake consolida-

tion with the development of an arrhythmic and polyphasic sleep-wake pattern (41). Also, as the dementia progresses, there is a gradual loss of Stage 2 EEG sleep transients (spindles and K-complexes), loss of slow wave sleep, diminution in REMs (42), and development of more severe sleep-disordered breathing (43). The latter may pose an added burden to the already impaired mental status of Alzheimer victims. Alzheimer patients characteristically do not show the short REM latency seen in elderly patients with major depression or the extent of sleep continuity impairment and early morning awakening. The distinctive sleep findings of depression and Alzheimer's dementia may have utility in differential diagnosis and prognosis for elderly patients with mixed depression and cognitive impairment (44).

Patients with generalized anxiety disorder appear to share with depressives sleep continuity disturbance as well as reduced slow wave sleep. In contrast, a reduction of REM sleep percentage and an absence of short REM sleep latency appear to characterize patients with generalized anxiety disorder, in contrast to the sleep of major depression (35). Data on the sleep patterns of patients with anxiety disorders other than generalized anxiety have also begun to emerge in the last 5 years. Some patients with panic disorder–agoraphobia demonstrate diminished sleep continuity and slow wave sleep, but do not appear as a group to show the REM sleep stigmata of major depression (45). It seems likely, however, that the sleep of panic disorder patients will evidence considerable heterogeneity, perhaps related to a personal or family history of major depressive disorder, as is frequently the case. Thus, panic disorder patients with a family history of major depression or with a vulnerability to major depression may be more likely to evidence a short REM sleep latency than panic patients without such a personal or family history. Moreover, Dube et al. (46) have suggested that panic disorder patients with a history of major depression or a family history of depression are more likely to evidence cholinergic supersensitivity, as measured by arecoline REM induction responsiveness.

Finally, concerning the specificity of EEG sleep changes in depression, we investigated whether sleep in depression and narcolepsy is basically similar or shows systematic and reliable differences (47). The question is of interest to sleep researchers, because depression has been reported as frequent in narcolepsy and has been considered to be either a reaction to chronic sleepiness or alternatively an endogenous expression of the pathophysiology of narcolepsy. Supporting the latter possibilities are reports of similarities between the nocturnal REM sleep of narcoleptics and patients with endogenous depression. Compared with outpatient major depressives who were age matched, the nocturnal sleep of narcoleptics was found to be characterized by a shorter sleep latency (both before and after age 40 years), more wakefulness after sleep onset (after age 40), shorter REM latency (before age 40), greater Stage 1 sleep percentage (before and after age 40), and greater first REM period activity (after age 40). While REM latency was shorter in both groups relative to expected values from age-matched healthy controls, nonetheless, the distribution of REM latency values appeared different from that of the outpatient major depressives because of the very high frequency (48%) of SOREMPs in the narcoleptics. These differences in nocturnal sleep between depressives and narcoleptics are similar in some respects to differences between the two groups in measures derived from the daytime multiple sleep latency test (MSLT). The MSLT reveals a shorter sleep onset in narcoleptics than in depressives as well as a much greater frequency of SOREMPs (48). Furthermore, the concurrence of narcolepsy with sleep apnea and/or nocturnal myoclonus has frequently been noted, while

sleep apnea and nocturnal myoclonus appear to occur no more often in the sleep of depressives than in the normal population (49).

In summary, the published data taken as a whole suggest the relative specificity of the sleep changes seen in depression, particularly those occurring in the first NREM-REM sleep cycle. Clearly, however, much additional research, particularly in the anxiety and the psychotic disorders (including schizophrenia), is needed before the issue of specificity will be resolved.

Further studies of REM latency variability in depression

Sleep research in affective illness has used different definitions of REM latency. As previously noted by Knowles et al. (50), measurement of REM latency has varied considerably across laboratories, depending on the definition of sleep onset employed, the inclusion or exclusion of wake time during the first NREM sleep period, and the definition of the first REM period. The concurrent validity of different definitions of REM latency has been tested by comparing the ability of each definition to discriminate between primary major depressives (outpatients and inpatients) and healthy controls (33). In outpatients the percentage of cases correctly identified by REM latency ranged from 62.5–70.8%, and in inpatients the range of sensitivity was 64.6 to 70.8%. REM latency definitions with the least stringent sleep onset criteria yielded the lowest specificity. However, different definitions of REM latency correlated about equally well with Hamilton depression ratings ($r = -0.70$), showing a significant inverse relation (that is, the greater the Hamilton depression score, the shorter the REM latency).

REM latency variability in depression has also been addressed in several other recent studies. The extent of increase in REM latency from the first to second night (so-called "paradoxical evolution") in major depression correlated significantly with increasing duration of current episode, earlier age of onset, and poorer clinical response to tricyclic antidepressants (51). These results suggested that REM latency in major depression may show significantly different patterns of night-to-night variability and that such within-subject variability appears to correlate with important clinical aspects of the disorder.

Another recent study of REM latency distribution in major depressives examined the clinical characteristics associated with the finding of SOREMPs (30). Earlier, Coble et al. (31) suggested that the presence of SOREMPs in depressed patients generally predicted an inadequate response to tricyclic antidepressants and the need to use combination chemotherapy (tricyclics plus phenothiazines). Similarly, Kupfer et al. (52) reported that delusional depressives who were nonresponders to either amitriptyline or combined therapy, and thus required electroconvulsive therapy, exhibited much shorter REM latencies than did pharmacological treatment responders. In a recent revisit of these issues. Ansseau and colleagues (30) examined REM latency distribution in a sample of 92 major depressives. It was found that REM latency showed a continuous unimodal rather than bimodal distribution, with a peak frequency of REM latency values between 50 and 59 min on each of 4 consecutive nights. A total of 20 patients from this sample (21.6% of patients studied) exhibited at least one SOREMP, i.e., a REM latency of $\leq$10 min. SOREMP-positive major depressives were older at the time of study and at the age of onset of depressive illness than the remainder of this sample, who were SOREMP negative. This finding was consistent with that of Reynolds et al. (28), who reported in an independent sample of elderly depressives that the frequency of SOREMPs was extremely high, even in the absence of delusional depression. Fi-

nally, it has recently been shown that internight variability in REM latency in patients with major depressive disorders is positively and significantly related to advancing age and with age at onset of depressive illness (53). At the same time, gender may contribute significantly and independently of age to REM latency internight variability. Thus, in the Ansseau study (53), male patients showed more internight variability in REM latency than did female patients when age was controlled. This is the first demonstration of the potential importance of gender in determining EEG sleep characteristics of major depressive illness. However, the extent to which gender may be an important source of variance in other sleep measures has yet to be investigated systematically in depressive patients.

Aging and sleep in depression

The sleep characteristics of depression reflect robust interactions between age and disease (23,24). The sleep changes that characterize depression also occur, to a lesser extent, during the course of healthy aging. In particular, the age-dependent increase in wakefulness after sleep onset and the decrease in slow wave sleep characterize both healthy aging and depressive illness. It is not yet clear if REM latency itself shortens during the course of normal aging and, if so, how robust this trend may be. In samples of depressed patients, REM latency shows a linear decrease with advancing age (24). On the other hand, the tendency for REM sleep periods to become progressively longer during the night is also significantly diminished in middle-aged and older persons compared with healthy young adults (54). It is precisely the shortening of REM sleep latency and the altered intranight temporal distribution of REM sleep, with greater amounts of early REM sleep, that most specifically characterize the sleep of patients with major depression.

During the last 5 years, additional data on the sleep of childhood and elderly depressives have been published, and these data lend further support to the concept of an interaction between aging and disease in determining the sleep physiological abnormalities of depression. In a large study of prepubertal children with major depression, Puig-Antich et al. (55) reported few differences between the sleep of depressed prepubertal children and healthy controls matched for age, sex, and pubertal status. On the other hand, when the depressed children were subsequently restudied during clinical remission, their REM latency showed a shortening compared with the controls (56). More recently, Lahmeyer et al. (57) have suggested that the sleep of adolescents with major depression is characterized by a constellation of findings similar to that of adult major depressives, particularly shortening of the first REM sleep period.

At the other end of the life cycle, it has been demonstrated that very short REM sleep latencies, prolonged first REM periods, and extreme sleep maintenance difficulty reliably characterize the sleep of elderly nonbipolar and nondelusional, predominantly endogenous elderly depressives (28). One of the more interesting findings to emerge from these studies has been the high frequency of SOREMPs in elderly endogenous depressives, where ~43% of REM latency values are <10 min. This finding stands in contrast to rates of 1.4% in healthy controls and 17% in nondepressed probable Alzheimer-demented patients. The sleep maintenance difficulties of the elderly depressives were found to be significantly correlated with the severity of depression, as indicated by Hamilton ratings.

To clarify further the nature of age-dependent changes in the sleep of depressed patients, additional normative sleep data across the life cycle, quantified by computer,

are necessary. Expansion of the normative database in this fashion will permit a more careful delineation between depressives and controls with respect to the rates of age-dependent "decay" of sleep maintenance and slow wave sleep as well as alterations in REM sleep distribution. It is likely that differences between the sleep of depressives and controls will be significantly influenced by the age of the samples studied. Younger depressives differ from controls more in measures of sleep initiation difficulty, for example, while older depressives differ more from controls in measures of sleep maintenance difficulty (58). The interaction of age and disease in determining the sleep physiological abnormalities of depression will be more intensively examined during the next decade of psychiatric sleep research.

EEG sleep alterations during acute antidepressant therapy

EEG sleep measures are useful in monitoring the neurophysiological effects of tricyclic antidepressants (59), in the prediction of treatment response (8–10,60), and in the prediction of vulnerability to relapse (7). All-night sleep recordings during treatment have shown that amitriptyline, desipramine, and zimelidine all produce rapid suppression of REM sleep, as evidenced by prolongation of REM latency, reduction of REM activity, and decrease in percentage of REM sleep (61,62). Tonic aspects of REM sleep, such as REM sleep latency and REM sleep percentage, tend to remain suppressed for weeks or longer during maintenance treatment. In contrast, tolerance to suppression of REM activity appears to develop over several weeks of treatment, as evidenced by the return of phasic REM activity.

Kupfer et al. (8,60) showed that clinical response to amitriptyline in 82 depressed patients could be predicted from the amount of REM sleep suppression and REM latency prolongation during the first 2 nights of treatment. Gillin et al. (9) obtained similar results in six depressives. More recently, Hochli and colleagues (10) have reported that the extent of clomipramine-induced REM sleep suppression is correlated with eventual clinical response in 10 patients with major depression. Thus, there are now at least three reports suggesting that the amount of REM sleep suppression on the first night of drug therapy is a good predictor of clinical response.

Both amitriptyline and zimelidine appear to strengthen the rate of production of delta activity in the first NREM period, thereby moving the distribution of delta activity during the night in a normal direction. Antidepressant drug effects appear to be most evident during the first NREM-REM cycle of the night. Moreover, patients who respond to amitriptyline show a greater REM sleep suppression than do nonresponders, as well as a greater prolongation of REM latency, during the first 2 nights of drug administration (52). Final clinical response is significantly correlated with the extent of acute reduction in REM sleep percentage and prolongation of REM sleep latency during the first 2 nights of treatment with amitriptyline.

In contrast to the improved sleep latency and sleep continuity induced by amitriptyline, desipramine administration is associated with somewhat worsened sleep continuity, particularly after 1 week of drug administration with a dosage of 150 mg daily (62). Similar to amitriptyline, desipramine induces a rapid suppression of REM sleep with partial tolerance observed in measures of phasic REM activity after 3 weeks of treatment.

Monitoring the acute effects of antidepressants on sleep is useful not only with respect to predicting treatment response. Increasingly, psychiatric sleep research is characterized by the use of antidepressants with more specific neuropharmacologic activi-

ties, such as desipramine, which is a relatively specific noradrenergic reuptake blocker; or zimelidine, which is a relatively specific serotonin reuptake blocker. The use of such specific probes, which are at the same time antidepressants, will permit one to test hypotheses concerning monoamine system changes in the pathogenesis of depression, in the sleep-wake dysregulation of depression, and in the neurobiology of recovery.

MODEL OF SLEEP AND MOOD REGULATION IN AFFECTIVE ILLNESS (TABLE 2)

During the last decade, sleep research in affective illness has relied increasingly on the use of experimental manipulations, both pharmacologic and naturalistic, to understand possible underlying mechanisms (for review, see ref. 63). Examples of such manipulations have included the use of specific pharmacologic probes, sleep deprivation, REM deprivation, and phase advancement of the sleep-wake cycle. For example, studies by Sitaram and colleagues (64) and by Gillin et al. (65) have tested the cholinergic supersensitivity hypothesis of affective disorders by infusing the cholinergic muscarinic agent arecoline during the second NREM period. These investigators have found that affective disorder patients predictably show a more rapid onset of the second REM period than do nonaffective disorder and healthy controls. This abnormality appears to be both state-like and trait-like. The differential REM induction responsiveness of depressive patients to arecoline has been viewed within the context of a hypothesized imbalance between cholinergic and monoaminergic activity, as recently reviewed by McCarley (66). In humans REM latency has also been shortened by oral administration of the muscarinic agonist RS-86 before bed (67,68) and by intravenous administration of physostigmine or arecoline during the first NREM period. Scopolamine has been found to block the REM-inducing effects of arecoline: Gillin et al. (65) have developed a model of muscarinic supersensitivity in normal volunteers, induced by 3 days of scopolamine administration for 3 mornings. These volunteers developed the major sleep disturbances of depression, including short REM latency, increased REM density, and reduced total sleep time, but they did not develop symptoms of depression.

Another body of research has linked EEG sleep abnormalities in depression to disturbances of biological rhythm. Wehr and Goodwin (32) have suggested that the onset of REM sleep, the distribution of REM sleep density, body temperature, and cortisol levels may be abnormally phase advanced in depression. No consensus on this issue has developed, however. Two of the primary difficulties to date have been infrequent sampling and insufficient total time studied. Statements about the internal phase relations of the body temperature rhythm require a sampling frequency sufficient to draw the precise shape of the cycle; the reason for this is that subtle changes in the wave form, period, or amplitude may appear to indicate phase changes.

Moreover, as Avery and colleagues (69) have suggested, it is clear that sleep itself

TABLE 2. *Paradigms of sleep and mood regulation in depression*

REM sleep disinhibition model (11)
Phase advance hypothesis (32)
Two-process model (34,71)
Cholinergic supersensitivity hypothesis (9,64,65)

affects the circadian temperature rhythm. It is possible, therefore, that sleep and/or its disruptions as seen in depression mask the underlying temperature rhythm. In fact, evidence of a decrease in temperature rhythm amplitude in depressed patients has been reported by Avery et al. (69), who observed a higher mean nadir in the nocturnal temperature rhythms of depressives, and by Schulz and Lund (70), who found that endogenous depressives with SOREMPs showed smaller differences between daytime and nighttime core body temperature and thus demonstrated smaller variation around the daily mean value. If the underlying phase advance of circadian temperature rhythm hypothesized in depression is masked by the disturbed sleep-wake cycle itself, this suggests that the use of sleep deprivation in a constant-routine protocol may be a useful approach to "unmasking" the circadian temperature rhythm in depression.

Borbély's two-process model (34) of sleep-wake regulation in depression provides a second perspective on the biology of depression. This model suggests that the sleep changes of depression depend on the interaction of two separate processes affecting the timing and organization of sleep. Process "S" is indexed by sleep propensity and reflects an hypothesized sleep factor that accumulates during wakefulness and is dissipated by sleep. Process "S" is broadly indexed by slow wave sleep (or, more precisely, EEG power in the slow wave spectrum) and by sleep initiation and maintenance. Process "C" is a circadian process that is reflected in REM sleep propensity and is also evidenced by the circadian temperature rhythm. The model posits that Process "S" is specifically deficient in depression, as evidenced by the overall short sleep time, sleep maintenance difficulties, prolonged sleep latency, reduced slow wave sleep and EEG delta wave activity (particularly in the first NREM period), the earlier appearance of REM sleep, and the clinical benefits of sleep deprivation. Specifically, the Borbely model attempts to address the question of whether there is a mutual interaction between the process of sleep regulation and the symptoms of depression (71). In other words, it attempts to account for both the depressive sleep pattern and the antidepressant effect of sleep deprivation. Borbély's hypothesis posits that the sleep-dependent process of sleep regulation (namely, Process "S") is deficient in depression; thus, impairment in sleep onset and sleep maintenance in depression and diminution of slow wave sleep are attributed to reduced sleep propensity, a consequence of a low level of Process "S." Hence, also, REM sleep is disinhibited or allowed to appear earlier after sleep onset. The model thus predicts that an increased level of Process "S," attained by sleep deprivation, should be correlated with clinical improvement following sleep deprivation. In other words, depressed patients who improve symptomatically following sleep deprivation should also show improvement in sleep initiation and maintenance and increased slow wave sleep during recovery sleep. Conversely, if clinical improvement after sleep deprivation is not accompanied by improved sleep continuity and enhanced slow wave sleep, this would suggest that Process "S" is not relevant to the regulation of mood in depression. To test this prediction, we recently carried out a sleep deprivation experiment in 15 hospitalized endogenously depressed patients (72). As predicted by the model, responders to sleep deprivation (but not nonresponders) showed significant improvement in sleep latency, sleep efficiency, and slow wave sleep during recovery sleep.

The Borbély model also may explain age-dependent changes in the sleep of depression. We speculate that the waning ability to sleep, which characterizes both normal aging and, to a much greater extent, depression, may reflect a greater vulnerability of Process "S" to aging, while Process "C" is more age resistant or stable. At the same

time, however, it should be remembered that Process "S" is more of a concept at this time than an identified substance or physiological process, and it is currently inferred from EEG analysis. Nevertheless, the integration of theory and clinical observation achieved in this model has been an advance in psychiatric sleep research.

A final and promising area of investigation in sleep and the pathophysiology of depression is exemplified by the work of Mirmiran and colleagues (73), which has attempted to produce an animal model of the sleep abnormalities of depression. These investigators have reported that treatment of rat pups in the early postnatal period with chlorimipramine results later in the adult animal having EEG sleep structural abnormalities similar to those of humans with major depression. Moreover, the animals are reported to show a constellation of behavioral changes that have been suggested to resemble certain symptoms of depression. Confirmation and extension of these observations appear to hold considerable promise in elucidating the pathophysiology of sleep changes in depression.

SUMMARY AND CONCLUSIONS

Future sleep research in affective illness will probably continue the current evolution beyond cross-sectional to longitudinal studies, and beyond a largely descriptive emphasis to the testing of specific hypotheses and predictions derived from models of the pathophysiology of depression. These models are and will be variously neurochemical, chronobiological, genetic, and developmental in nature. Adequate testing of these models and predictions from them will require the use of pharmacologic and naturalistic probes and the use of sophisticated CNS imaging techniques. These probes will help further characterize the physiology of depression under conditions of disequilibrium or perturbation, such as following sleep deprivation, REM deprivation, phase advancement of the major sleep period, or the administration of antidepressant drugs with specific monoaminergic activity.

Concurrently, if one is to understand further whether the sleep abnormalities of depression are part of a larger circadian rhythm disturbance, investigations will necessarily include 24-h measures of sleep-wake activity, psychomotor activity, and probably core body temperature rhythm under constant routine conditions. A complementary point of view would suggest that more intensive investigative efforts be focused on the first 100 min of sleep at night, since it is the first NREM-REM cycle that seems to show the greatest and most specific deviation in depressed patients from normal controls. Efforts to characterize further this part of the 24-h cycle, with respect to age- and gender-related variance as well as responses to physiologic, hormonal, pharmacologic, and naturalistic probes, are strongly warranted.

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