The Applied Use of Psychotherapy in the Study of the Psychobiology of Depression

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In an investigation of electroencephalographic (EEG) sleep in endogenously depressed outpatients before and after treatment with cognitive behavior therapy (CBT), a 79% response rate was observed in 38 patients completing the 16-week treatment protocol. Despite substantial improvements in symptoms, EEG sleep did not change significantly in recently remitted patients. Moreover, stability of sleep between pretreatment and post-treatment assessment was confirmed by highly significant correlations; this stability may indicate either the presence of slowly healing neurophysiological "scars" or potential trait markers of depression. EEG sleep correlates of endogenous depression were not correlated with poor response to CBT; however, sleep correlates of hypersomnia (an atypical feature of endogenous depression) were correlated with poorer outcome. These findings suggest that CBT and tricyclic antidepressants may share several common EEG sleep correlates of treatment responsivity.

Depression is an ideal condition for which to study psychobiological interactions: its syndromal characteristics include both vegetative and psychological dysfunction, and its etiology has been linked to both psychosocial and biological factors.[1] Nevertheless, despite clear conceptual grounds for conducting research that incorporates both biological and psychological domains, few such studies have been undertaken. In particular, essentially all studies investigating biological correlates of recovery from an episode of depression have utilized somatic antidepressant treatments.[2] The use of psychotherapy to treat patients in studies of the biological processes of depression offers several potential advantages over pharmacotherapy or electroconvulsive therapy. First, the natural progression of a biological disturbance can be tracked, from illness to remission, without the influence of somatic intervention. Thus, the process of recovery may be uncoupled from the direct effects of somatic treatment on the central nervous system (i.e., effects that may occur in all people exposed to the intervention, independent of their condition or response). Second, longitudinal studies of patients successfully treated with psychotherapy can be undertaken without the possible confounding physiological effects of rebound from discontinuation of pharmacotherapy or impending relapse provoked by premature withdrawal of medication. These advantages may be particularly useful for differentiation

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of biological disturbances that are trait-like (i.e., those that persist in recovery) from those that are state-dependent (i.e., those that normalize in remission).

However, there remains significant skepticism that psychotherapy can be used for such a purpose, in part because some evidence suggests that treatments such as cognitive behavior therapy (CBT)[3] may not be sufficiently effective in more severe depressive states.[4] Indeed, some investigators have predicted that patients manifesting abnormalities such as hypercortisolism or reduced rapid eye movement (REM) sleep latency may have an endogenous or autonomous illness that will respond poorly to psychotherapy and hence require somatic treatment.[5-12]

In this article, we describe the use of CBT to study the psychobiological correlates of depression across the recovery process. The Psychobiology of Recovery in Depression (PRD) project is, to our knowledge, the first project specifically designed to utilize a form of psychotherapy so that a biological process associated with depression (in this case, disturbances of sleep neurophysiology) can be studied longitudinally without the influence of somatic therapy. In this report we describe the feasibility of this type of integrative psychobiological research, and we test the specific hypothesis that patients with reduced REM latency, a well-replicated biological marker of endogenous depression,[7,9] will have a poorer outcome following CBT than patients with nonreduced (i.e., normal) values. In addition, we present preliminary findings concerning other electroencephalographic (EEG) sleep correlates of response and the post-treatment sleep of unmedicated, recently remitted patients.

METHODS

Patients eligible for this study were outpatients presenting to the Western Psychiatric Institute and Clinic. Patients initially were evaluated by a clinician-psychiatrist team, and if patients met the criteria of the DSM-III-R[13] for major depressive disorder, they subsequently were seen by our research team for a detailed secondary evaluation. This evaluation included medical history, physical examination, laboratory screening studies, and an independent research interview using the Schedule for Affective Disorders and Schizophrenia (SADS)[14] and the 17-item Hamilton Rating Scale for Depression (HRSD).[15]

On the basis of these evaluations, patients were eligible for the study if they 1) met Research Diagnostic Criteria (RDC)[16] for a diagnosis of primary major depression (nonbipolar, nonpsychotic subtype); 2) met RDC criteria for probable or definite endogenous subtype; 3) had HRSD scores ≥ 15; and 4) did not suffer from untreated or poorly controlled conditions that may cause depression (e.g., hypothyroidism), invalidate EEG sleep studies (e.g., sleep apnea), or require treatment with agents that may do either of these (e.g., corticosteroids or beta-blockers). Patients with antecedent minor or intermittent depressive disorder (including those who met DSM-III-R criteria for dysthymic disorder) also were excluded from the protocol, as were persons with either a history of active drug or alcohol abuse (either primary or secondary to the affective disorder during the two years prior to intake) or, at intake, severe personality pathology (i.e., borderline personality disorder and antisocial personality disorder). By excluding patients with more chronic and complicated depressive disorders, we hoped to maximize the opportunity to capture the psychobiological correlates of an episode of depression early in its course and shortly following resolution of the episode. Among the first 70 patients evaluated for eligibility by our research team, 46 met entry criteria and 44 agreed to research participation and provided written, informed consent.

Basic demographic data and clinical characteristics are shown in Table 1. Of these 44 patients, 6 (14%) did not complete the 16-week therapy protocol. Completers ($n = 38$) and dropouts did not differ significantly

on any of the measures studied. The remainder of this report deals with the 38 treatment completers unless otherwise specified.

Following intake assessment, patients began a 14-day medication-free observation period. During this time, patients were monitored to ensure that they were not using alcohol or other psychoactive substances and that their level of depression was persistent. While most patients were completely medication free, a small number of patients were permitted to remain on thiazide diuretics ($n = 3$) or well-stabilized dosages of insulin ($n = 2$). Upon completion of the 14-day period, patients still manifesting an HRSD severity level of ≥ 15 were assessed using the 21-item Beck Depression Inventory (BDI)[17] and the Global Assessment Scale (GAS).[18]

Patients next were studied for three consecutive nights in our outpatient Sleep Evaluation Center. The methods for conducting and scoring EEG sleep studies have been described in detail elsewhere.[9] Analyses of hand-scored EEG sleep yield 20 variables that cover different aspects of sleep maintenance, sleep architecture, and REM sleep. Our primary analyses focused on the four most widely replicated EEG sleep features of endogenous depression: poor sleep efficiency (a measure of the ability to fall asleep and stay asleep: time spent asleep divided by total recording period, multiplied by 100); diminished slow-wave sleep (percentage of "deep" or delta sleep: the sum of time spent in sleep stages 3 and 4 divided by time spent asleep, multiplied by 100); increased REM density (a measure of the activity of rapid eye movements per minute of REM sleep); and reduced REM latency (the early onset of the first REM period: the amount of time elapsed from the initiation of Stage 2 sleep until the first 3-minute episode of REM sleep, minus minutes of intervening wakefulness).[9] These four measures are not highly intercorrelated and reflect different aspects of EEG sleep disturbance in depression.[9] Although such sleep disturbances are not entirely specific to, nor pathognomonic for, depression, they are useful for discrimination of the sleep of depressed individuals from that of normal controls or persons with other psychopathological conditions.[9]

Sleep study results are reported as two-night means, allowing the first night for accommodation to the sleep laboratory. Criteria for abnormality on these measures vary somewhat from laboratory to laboratory and depend, in part, on the age range of the

TABLE 1. Demographic and clinical characteristics of patient population

Characteristic	n	%
Age (years) mean ± SD	37.5 ± 8.9	
Males	12	27
Females	32	73
Marital status		
Single, never married	15	34
Married	19	43
Separated/divorced	8	18
Widowed	2	5
Employment status		
Employed outside home	33	75
Home	4	9
Student	4	9
Unemployed	3	7
Education		
High school	9	20
College	26	60
Postgraduate	9	20
RDC Endogenous		
Probable	7	16
Definite	37	84
Duration of current episode		
< 3 months	8	18
3 months to ≤ 6 months	13	30
≥ 6 months to ≤ 1 year	14	31
1 year to 18 months	9	21
Age at onset (years) mean ± SD	29.9 ± 11.4	
Previous episodes		
None, 1st episode	17	39
1–2 prior episodes	15	34
3 or more prior episodes	12	27
Depression measures, mean±SD		
Hamilton Depression Rating Scale	21.6 ± 4.0	
Beck Depression Inventory	26.3 ± 7.4	
Global Assessment Scale	51.3 ± 7.9	

Note: Total number of patients = 44. SD = standard deviation.

sample and the nature of the comparison group.[9] For this sample, the following criterion scores for abnormality were established to reliably differentiate an independent sample of depressed patients from healthy, age-matched controls: poor sleep efficiency ≤ 89%; reduced slow-wave sleep, ≤ 10%; increased REM density (averaged for all REM periods), ≥ 1.5 units; and reduced REM latency, ≤ 60 minutes (M.E. Thase, unpublished data). In each case an "abnormal" value would be supportive of a diagnosis of endogenous depression.[9]

Following completion of pre-treatment EEG sleep studies, all patients began treatment with CBT. Therapy was conducted according to the manual of Beck et al.,[3] using a 16-week, 20-session protocol (twice-weekly sessions for 4 weeks, weekly thereafter). The therapists had completed at least 2 years of supervised training and had received external certification according to the standards established for use in the National Institute of Mental Health Collaborative Treatment of Depression Study.[19] Unlike the collaborative study, however, therapists received ongoing weekly supervision. During the course of treatment, patients were seen biweekly for independent assessments of symptomatic status according to the HRSD, GAS, and BDI. All ratings (as well as all therapy sessions) were conducted without knowledge of EEG sleep results. Patients received no psychotropic medications during the entire course of therapy. Post-treatment sleep studies were completed for 36 of the 38 patients (95%) immediately following the 16th week of treatment using the methods described above, including the 14-day drug- and alcohol-free interval.

Data pertaining to clinical outcome were analyzed in several ways. First, the sample was stratified into two subgroups consisting of patients with reduced ($n = 17$) or nonreduced ($n = 21$) pre-treatment REM latency. Changes in the continuous measures of depression (HRSD, BDI, and GAS) were compared between the reduced and nonreduced groups with a series of analyses of variance (ANOVAs) with repeated measures for time (pre- vs. post-treatment). Second, the number of patients who met a prespecified definition of response was determined using a three-stage criterion comparable to that employed in studies of antidepressant pharmacotherapy: 1) ≥ 50% reduction in HRSD scores, 2) a final score ≤ 10, and 3) response sustained for ≥ 2 weeks by week 16. To facilitate comparison with other trials, we also computed the number of patients who ended treatment with scores of ≤ 6 on the HRSD or ≤ 9 on the BDI.

Normalization of EEG sleep parameters first was assessed for all responders with a series of one-tailed, paired (pre-post) t-tests. Stability of sleep measures in responders was further assessed by calculating the correlations of pre- and post-treatment values. Finally, because "normalization" cannot be expected unless a patient both 1) had an abnormal value at pretreatment, and 2) no longer was depressed at the end of treatment, paired t-tests were repeated in subgroups of responders who met the aforementioned pretreatment criteria for poor sleep efficiency, diminished slow-wave sleep, increased REM density, or reduced REM latency.

RESULTS

The 38 patients who completed the trial showed highly significant improvements ($P < 0.001$) on all three symptom measures (see Table 2). Thirty patients (79%) met the three-stage response criterion; 29 patients ended treatment with HRSD scores ≤ 6 and 24 patients had final BDI scores of ≤ 9. Twenty-two patients (58%) met all three definitions of improvement. Reduced and nonreduced REM latency groups did not differ with respect to degree of symptomatic improvement on the HRSD at post-treatment (see Table 2 and Figure 1), nor on the GAS and BDI. As summarized in Table 2, the reduced and nonreduced REM latency groups also did not differ significantly on our three-

stage criterion for response or the proportion of patients with final BDI scores of ≤ 9. However, a trend difference ($P = 0.06$) was found on the remaining categorical definition: only 59% ($n = 10$) of those with reduced REM latency had final HRSD scores of ≤ 6, as compared to 91% ($n = 19$) of those with nonreduced REM latency (see Table 2).

Among the four key sleep measures, only percent of delta sleep correlated significantly with final HRSD scores (r, partialling age, = 0.40, $P < 0.01$). Contrary to our prediction, however, patients with reduced levels of slow-wave sleep showed greater improvement. An exploratory examination of the 16 remaining EEG sleep measures revealed an unanticipated set of additional correlates of outcome: longer total recording period ($P = 0.01$), increased sleep time ($P = 0.05$), increased REM time ($P = 0.001$), increased REM activity ($P =$

TABLE 2. Pre-treatment and post-treatment depression measures and treatment response rates

Continuous Measures[a]	Pre-treatment	Post-treatment
Total sample ($n = 38$)		
HRSD	21.6 ± 3.6	4.5 ± 4.6
BDI	26.7 ± 7.7	7.4 ± 7.6
GAS	52.0 ± 7.6	85.1 ± 12.7
Reduced REM latency ($n = 17$)		
HRSD	21.3 ± 3.3	5.0 ± 5.0
BDI	25.1 ± 7.9	5.8 ± 8.8
GAS	53.4 ± 8.8	83.4 ± 13.8
Nonreduced REM latency ($n = 21$)		
HRSD	22.0 ± 3.9	4.4 ± 4.4
BDI	28.0 ± 7.0	6.8 ± 8.3
GAS	50.9 ± 6.6	86.6 ± 11.9

Categorical Definition	Response[b]		HRSD≤ 6		BDI≤ 9	
	n	%	*n*	%	*n*	%
Total sample ($n = 38$)	30	79	29	76	24	63
Reduced REM latency ($n = 17$)	12	71	10	59	11	65
Nonreduced REM latency ($n = 21$)	18	86	19	91[c]	13	62

Note: HRSD = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; GAS = Global Assessment Scale. Values are means ± SD.
[a]ANOVA time factor, $P < 0.001$. No significant differences were found between reduced and nonreduced REM latency groups continuous outcome on these measures. REM latency classification did not correlate significantly with time.
[b]HRSD ≤ 10 + Δ% ≥ 50% + response criteria sustained for ≥ 2 weeks before week 16.
[c]$\chi^2 = 3.6$, df = 1, $P = 0.06$ (two-tailed; corrected for discontinuity).

FIGURE 1. Biweekly HRSD scores for responders with reduced ($n = 12$) or nonreduced ($n = 18$) REM latency

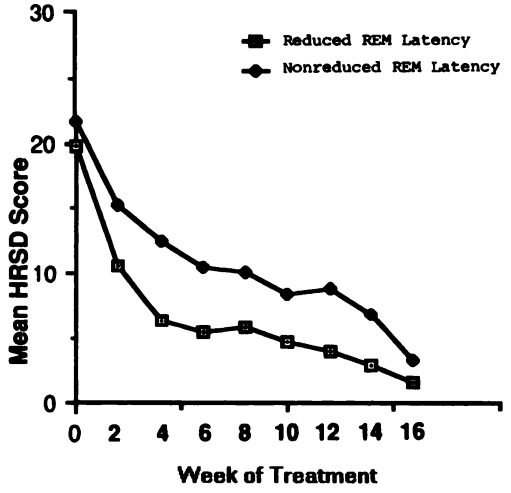
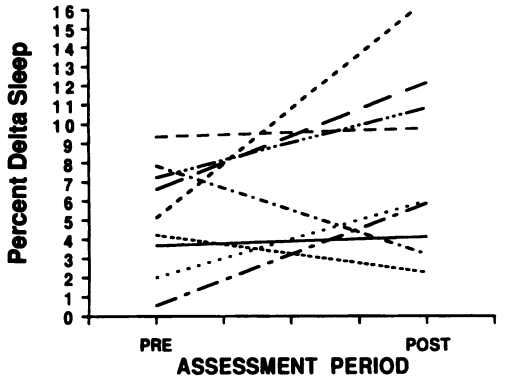


FIGURE 2. Pre- and post-treatment percentages of delta sleep in responders with pre-treatment disturbance



0.05), and greater number of REM periods ($P = 0.01$) were associated with higher final HRSD scores. When taken together with the slow-wave sleep finding, these six intercorrelated EEG sleep variables are best viewed as features of hypersomnia.[20]

Pre-treatment compared with post-treatment assessments of EEG sleep in patients who met response criteria are summarized in Table 3. None of the sleep measures changed significantly. Indeed, 18 of 20 measures showed substantial stability, as reflected by significant pre-post correlations. All four of the key sleep measures showed such stability: sleep efficiency, $P < 0.001$; delta sleep %, $P < 0.001$; REM latency, $P < 0.01$; and REM density, $P < 0.01$ (see Table 3). Analyses delimited to those patients who both started treatment with predetermined levels of EEG sleep disturbances and met response criteria revealed mixed results. There was a significant increase in delta sleep (%) among 14 affected patients (see Figure 2; $t = 3.3$, df= 13, $P < 0.01$). There also was a trend for REM latency values to increase ($P = 0.06$), but this marginal finding vanished when one case with extreme prolongation of post-treatment REM latency was removed from the analysis. Neither sleep efficiency nor REM density showed evidence of normalization.

DISCUSSION

The results from the first 38 patients to complete the PRD protocol demonstrate the feasibility of using a form of psychotherapy to conduct longitudinal studies of the psychobiology of depression. Several of the early findings from this project hold promise for clarifying relations between biological and clinical factors in depression. First, a large majority of patients in this series met criteria

TABLE 3. Pre- and post-treatment EEG sleep measures in recently remitted patients

EEG Sleep Variable[a]	Pre-treatment	Post-treatment	r
Total recording period, minute	435.2 ± 42.9	430.8 ± 42.7	0.38[b]
Sleep latency, minute	15.8 ± 9.3	14.6 ± 9.6	0.59[d]
Awake, minute	15.0 ± 15.3	19.2 ± 3.4	0.80[d]
Number of arousals	4.4 ± 2.6	4.1 ± 3.3	0.35
Awake: last 2 hours, minute	7.8 ± 8.2	9.6 ± 4.9	0.66[d]
Time spent asleep, minute	404.4 ± 40.7	396.9 ± 40.5	0.42[d]
Sleep maintenance, %	96.5 ± 3.4	95.5 ± 5.5	0.80[d]
Sleep efficiency, %	93.0 ± 3.6	92.2 ± 5.3	0.69[d]
Stage 1 sleep, %	4.2 ± 3.1	4.3 ± 3.1	0.42[b]
Stage 2 sleep, %	58.7 ± 8.9	58.5 ± 6.6	0.43[b]
Stage 3 sleep, %	6.3 ± 3.7	7.1 ± 2.9	0.16
Stage 4 sleep, %	6.5 ± 7.3	4.8 ± 6.2	0.71[d]
Delta sleep, %	12.8 ± 9.5	12.0 ± 6.8	0.61[d]
Non-REM sleep, %	75.7 ± 3.9	74.8 ± 4.7	0.63[d]
REM sleep, %	24.3 ± 3.9	25.2 ± 4.7	0.63[d]
REM time, minute	98.6 ± 20.3	100.7 ± 21.5	0.72[d]
REM activity, units	141.5 ± 49.6	138.2 ± 44.8	0.49[c]
REM latency minus awake, minute	68.0 ± 24.6	64.6 ± 15.7	0.46[c]
Number of REM periods	4.02 ± 0.74	3.88 ± 0.59	0.58[d]
REM density, units/min	1.43 ± 0.37	1.40 ± 0.39	0.55[c]

Note: Values are means ± SD.

[a]Two-night means (nights 2 and 3 versus nights 5 and 6), $n = 28$. None of the pre-post comparisons (paired t-tests) was significant.

[b]$P \leq 0.05$.

[c]$P \leq 0.01$.

[d]$P \leq 0.001$.

for response following treatment. A lower response rate (on the order of 50% to 60%) was anticipated because of the severity of symptoms in our sample, i.e., patients who would often be thought to require pharmacologic intervention. It therefore appears that, unlike the recent findings of the NIMH Collaborative Treatment of Depression Study,[4] moderately to severely depressed outpatients can be treated with CBT in some settings with excellent results. Since the Western Psychiatric Institute and Clinic was a research site for the Collaborative Treatment Study and our patients were drawn from the same basic referral population, direct comparisons between these studies may prove informative. We have suggested elsewhere[21] that the exclusion of more chronic cases, the availability of regular on-site supervision, and provision of "open label" therapy in a specialty clinic may have resulted in the differences in response observed in the two protocols.

Second, although the high degree of improvement observed in the current study resulted in a relatively small number of nonresponders available for study at the posttreatment stage, an unanticipated association emerged between EEG sleep measures of hypersomnia and poor response. This finding appears to parallel the long-standing clinical impression that hypersomnic patients also show a poorer response to tricyclic medication.[12] By contrast, only one marginal finding supported traditional views of "biological" depression; namely, a trend for a smaller proportion of patients in the reduced REM latency group to end treatment with HRSD scores of ≤ 6. This trend, if replicated, could be of clinical significance, because reduced REM latency has been reported to predict favorable response to tricyclic pharmacotherapy.[22,23] However, it should be noted that the reduced and nonreduced REM latency groups did not differ significantly on five other analyses of outcome. Moreover, Jarrett et al.[24] recently reported equivalent response to CBT in subgroups of depressed patients with reduced and nonreduced REM latency.

Third, the relative lack of change in the sleep of recently remitted patients provides little support for the view that EEG sleep disturbances are state-dependent features of depression. Only the percentage of slow-wave sleep significantly improved, and this finding was limited to the subgroup of 14 responders who had manifested low levels of delta sleep prior to treatment. The stability documented on a great majority of measures suggests that EEG sleep disturbances may persist into the early stages of recovery (as traits or "scars" of a depressive episode). Conversely, the process of biological recovery may lag behind clinical recovery by weeks or even months. The former position is supported by the recent report of reduced REM latency in first-degree relatives of depressed probands,[25] while the latter is suggested by a recent small study in which complete normalization of EEG sleep abnormalities was found after three years of sustained recovery.[26] Alternatively, it may be that our sample did not include a sufficient number of patients with extremely abnormal sleep profiles to enable proper testing of the hypothesis of state-dependent reversibility.

Beyond the need for replication, which we will accomplish by enrollment of a second cohort of 40 outpatients, these findings point to several directions for future research. First, it should be noted that our protocol did not include control groups to provide direct comparisons with patients randomly assigned to tricyclic pharmacotherapy or placebo. Without such comparison groups, it is impossible to discriminate correlates of spontaneous remission from more general indicators of treatment responsivity or from more specific predictors of CBT outcome. These findings therefore must be placed in the context of other research on response prediction. Second, we have initiated a follow-up protocol to track our patients' longitudinal course in order to assess potential psychobiological risk factors for relapse and EEG sleep following longer periods of sustained remission. Third,

the apparent utility of CBT in a sample with probable or definite RDC endogenous depression has led us to extend this paradigm to study even more severely depressed samples. In this regard, we have developed a treatment manual for inpatient CBT[27] and have conducted a pilot study of the utility of CBT as a primary treatment of hospitalized major depressives.[28] This study will permit an even broader exploration of the psychobiological correlates of psychotherapy responsivity, including other severity-linked markers of depression (e.g., hypercortisolemia or dexamethasone response) and comparisons with pharmacotherapy. Finally, when we are able to pool data from our inpatient and outpatient series, it will be possible to study patients across a wide range of clinical severity. Because the ultimate sample size will exceed 100 patients, it will be possible to conduct more complex multivariate analyses in order to address the possibility of higher-order interactions between clinical and EEG sleep variables. Such analyses will help to maximize the detection of possible subgroup distinctions and thereby permit evaluation of both the unique and the additive effects of clinical and biological factors in relation to recovery from major depression.

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Schizophrenic Patients' Attitudes to Therapists Using Behavioral and Holistic-Humanistic Techniques

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In a preliminary study of patients' perceptions of therapists' styles, 18 subjects with diagnoses of schizophrenia were randomly assigned either to social skills training or holistic health therapy. Four therapists conducted each treatment session in pairs, rotating between treatment conditions daily. At the end of 10 weeks of treatment, patients were able to discriminate among therapists on three interactional styles—"understanding," "independence-encouraging," and "critical-hostile"—and were able to differentiate between behavioral and holistic health treatments on "authoritarian" attitudes.

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