Which Depressed Patients Will Respond to Interpersonal Psychotherapy? The Role of Abnormal EEG Sleep Profiles

Michael E. Thase, M.D., Daniel J. Buysse, M.D., Ellen Frank, Ph.D., Christine R. Cherry, M.S., Cleon L. Cornes, M.D., Alan G. Mallinger, M.D., and David J. Kupfer, M.D.

Objective: *The authors tested the hypothesis that patients whose episodes of major depression evidenced more neurobiological disturbance would be less responsive to psychotherapy.* *Method:* *The study subjects were outpatients who were given a diagnosis of recurrent major depressive disorder (unipolar or bipolar II), according to the Research Diagnostic Criteria, following an interview with the Schedule for Affective Disorders and Schizophrenia. They were classified into a group with normal sleep profiles (N=50) and a group with abnormal sleep profiles (N=41) on the basis of a validated index score derived from three EEG sleep variables monitored for 2 nights: sleep efficiency, REM latency, and REM density. The groups' responses to short-term interpersonal psychotherapy were compared by means of chi-square tests and life table and random effects model analyses. Responses to the addition of pharmacotherapy for subjects who did not respond to interpersonal psychotherapy were also compared.* *Results:* *The patients with abnormal sleep profiles had significantly poorer clinical outcomes with respect to symptom ratings, attrition rates, and remission rates than the patients with more normal sleep profiles. Seventy-five percent of the patients who did not respond to interpersonal psychotherapy had remissions during subsequent pharmacotherapy.* *Conclusions:* *These findings help to define further a neurobiological "boundary" that may limit response to psychotherapy in depression. An abnormal sleep profile may reflect a more marked disturbance of CNS arousal that warrants pharmacotherapy.*

(Am J Psychiatry 1997; 154:502–509)

It has long been argued that the milder depressions, particularly those characterized by mood reactivity, interpersonal difficulties, and/or "neurotic" traits, are treatable with psychotherapy, whereas somatic strategies are the treatment of choice for the more severe or endogenous depressive disorders (1–5). Such observations date back over 80 years, spanning the seminal work of Kraepelin (1) and Gillespie (2) and the introduction of ECT and successive generations of antidepressants (3–5). This approach is reflected in ICD-10 (endogenous depression) and DSM-IV (melancholia), as well as the practice guidelines published by the Agency for Health Care Policy and Research (4) and the American Psychiatric Association (5). Although surprisingly few empirical data have emerged from controlled clinical trials in support of these impressions (4, 6, 7), many experienced clinicians remain convinced that the more endogenous depressions *require* somatic antidepressant interventions. Thus, continued efforts to identify differential predictors of response to psychotherapy and pharmacotherapy are worthwhile.

One problem hampering this line of research is the lack of consensus about the particular constellation of signs, symptoms, and historical correlates that best defines the construct of endogenous depression (8, 9). The reliability of potentially important criteria such as "distinct quality of mood," "loss of mood reactivity," and "pervasive anhedonia" also may be problematic (10). A third problem stems from the fact that a large proportion of depressed outpatients present with an admixture of endogenous and reactive characteristics (11, 12).

Laboratory methods may provide a more objective assessment of the pathophysiology of depressive disorders (13, 14). For example, the relation between hypothalamic-pituitary-adrenocortical (HPA) axis activity and response to various forms of therapy has been studied extensively (15). An abnormal response to the

Received July 8, 1996; revision received Oct. 31, 1996; accepted Dec. 4, 1996. From the Department of Psychiatry, University of Pittsburgh School of Medicine. Address reprint requests to Dr. Thase, Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213.

Supported in part by NIMH grants MH-41884 (Dr. Thase), MH-49115 (Dr. Frank), and MH-30915 (Dr. Kupfer) and a grant from the John D. and Catherine T. MacArthur Foundation.

The authors thank the staff and faculty of the Depression and Manic Depression Prevention Clinic and the Sleep Evaluation Center, Joel Greenhouse, Ph.D., Victoria Grochocinski, Ph.D., Ms. Lisa Stupar, and Ms. Janice J. Jozefov for their contributions to this work.

dexamethasone suppression test (DST) has been consistently associated with a proper response to placebo (15). To date, four studies have addressed the relation between HPA activity and response to psychotherapy (16–19). In two uncontrolled inpatient studies, measures of increased HPA activity predicted poorer responses to individual supportive psychotherapy (16) or cognitive therapy (19). In two controlled outpatient studies, subjects who were nonsuppressors on the DST had significantly poorer responses to group (17) or individual (18) cognitive therapy than suppressors. Therefore, increased HPA activity may indicate a greater need for active somatic treatment, although the relatively low prevalence of this abnormality in outpatients limits practical utility.

In comparison with disturbances of HPA activity, abnormalities in all-night EEG sleep studies are more common among depressed outpatients (20, 21). Reduced REM sleep latency is the most widely replicated EEG sleep variable associated with clinical diagnoses of endogenous depression (20–23), and both uncontrolled studies (24, 25) and controlled studies (26–29) suggest that patients with reduced REM latency may respond poorly to placebo and/or favorably to antidepressants. Reduced REM latency also has been associated with a greater risk of relapse into depression (30). However, six studies have examined response to various forms of psychotherapy in patients with reduced REM latency, and none has found a significant relationship (17, 31–35). Several lines of evidence now indicate that reduced REM latency, by itself, may be more a trait-like correlate of vulnerability to depression than a state-dependent "marker" of endogenous depression (36–38). Thus, the combination of reduced REM latency and other more state-dependent neurobiological correlates, such as poor sleep efficiency, increased phasic REM sleep, and hypercortisolemia, is necessary to identify depressed patients who "require" pharmacotherapy instead of psychotherapy alone.

To test this hypothesis, a composite EEG sleep profile (defined by REM latency, REM density, and sleep efficiency) was identified and validated in a study comparing depressed inpatients, depressed outpatients, and normal control subjects (39). Although only 44% of a group of 90 depressed outpatients were characterized by abnormal EEG sleep profiles, these patients had significantly poorer responses to cognitive behavior therapy than patients with more normal profiles (40). Further, during longitudinal follow-up, patients with abnormal sleep profiles were significantly less likely to recover fully and were significantly more likely to suffer recurrent depressive episodes (40).

Replication of these findings is necessary, and it should be determined whether EEG sleep abnormality also predicts poor response to other forms of psychotherapy. Specifically, if the effect of an abnormal EEG sleep profile is mediated by state-dependent deficits in neurocognitive functioning (40), a therapy emphasizing interpersonal factors may not be adversely affected. Indeed, in the National Institute of Mental Health Treatment of Depression Collaborative Research Program study (41), patients with higher pretreatment severity scores on the Hamilton Depression Rating Scale (42) had a poorer response to cognitive behavior therapy but not to interpersonal psychotherapy (43). It is also important to test a corollary prediction of this hypothesis, namely, that patients with abnormal sleep profiles will respond favorably to antidepressant pharmacotherapy.

This article addresses the relation between EEG sleep profiles and response to interpersonal psychotherapy in unmedicated outpatients with recurrent depressive disorders. Although the study design did not include a parallel group receiving pharmacotherapy, patients who did not respond to interpersonal psychotherapy were routinely treated with a standardized course of antidepressant medication.

METHOD

The study group included patients between the ages of 20 and 59 years; all provided explicit written informed consent. All of the patients were diagnosed as having a recurrent nonpsychotic major depressive disorder, either unipolar or bipolar II subtype, according to the Schedule for Affective Disorders and Schizophrenia (44) and the Research Diagnostic Criteria (45). Subjects were required to have had at least one previous episode of major depression, with the previous episode occurring within 2.5 years of the index episode and being separated by at least 10 weeks of intervening remission. A score of 15 or more on the 17-item Hamilton depression scale (42) was also required at the time of initial evaluation.

Patients meeting criteria for bipolar I disorder were excluded, as were those with rapid-cycling bipolar II disorder. Patients with a history of other serious comorbid DSM-III-R axis I diagnoses (e.g., obsessive-compulsive disorder, panic disorder, and substance abuse disorders) within the previous 5 years also were excluded. In addition, patients with well-established diagnoses of severe borderline personality disorder and/or antisocial personality disorder were excluded. This axis II exclusion criterion was based on our experience that such patients are less likely to adhere to treatment and research procedures.

Histories were taken, and physical examinations and laboratory studies (CBC, electrolytes, BUN, creatinine, glucose, thyroid function, liver enzymes, urinalysis, and ECG) were performed. Patients with active medical problems were excluded from the study, but those with minor or well-controlled problems (e.g., treated hypothyroidism or stabilized essential hypertension) were eligible if they were not taking medications with substantial psychotropic effects.

A total of 219 patients were screened for the study; 64 did not meet the psychiatric diagnostic criteria, 11 did not meet the depression severity criteria, two had a major or unstable medical disorder, six refused to undergo sleep studies or other study procedures, two received immediate treatment because of active suicidality, 13 requested treatment with medication, and 27 had other reasons for exclusion. Of the 94 patients who were accepted into the study, data on 91 are included in this report; two patients were not studied in the sleep laboratory because of shift work, and one dropped out after only a single night of study. The final study group included 76 patients with unipolar major depression and 15 patients with probable or definite bipolar II disorder.

All 91 patients underwent two consecutive nights of EEG sleep recording after completion of the baseline clinical evaluations. Subjects kept their habitual sleep and wake times for these sleep studies and were instructed not to use alcohol or medications known to affect sleep for 14 days before the studies. The sleep studies included a routine polysomnographic montage consisting of one channel of EEG recording (C3 or C4, referenced to A1-A2), bilateral electro-oculograms (EOGs) (referenced to A1-A2), and bipolar submental electromyograms (EMGs). The high- and low-frequency filter settings

TABLE 1. Demographic and Pretreatment Clinical Characteristics of Patients With Major Depression and Abnormal or Normal Sleep Profiles

Variable	Total Group (N=91)		Patients With Abnormal Sleep (N=41)		Patients With Normal Sleep (N=50)	
	N	*%*	*N*	*%*	*N*	*%*
Sex						
Male	26	29	11	27	15	30
Female	65	71	30	73	35	70
Marital status						
Married	36	40	17	41	19	38
Other	55	60	24	59	31	62
Race						
White	86	95	39	95	47	94
Black	5	5	2	5	3	6
Diagnosis						
Unipolar	76	84	32	78	44	88
Bipolar II	15	16	9	22	6	12
RDC definite endogenous type	57	63	27	66	30	60
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age at start of study (years)	35.3	8.8	36.8	8.6	34.0	8.7
Education (years)	15.7	1.7	16.0	1.5	15.4	1.8
Duration of index episode (weeks)[a]	23.0	19.3	17.7	11.3	27.4	23.2
Age at onset (years)	24.2	7.4	25.0	7.4	23.6	7.3
Number of previous episodes	5.3	5.7	5.6	5.7	5.0	5.7
Previous wellness interval (weeks)	53.9	41.0	56.3	37.6	52.0	43.7
Baseline Hamilton depression score						
17-item scale	19.6	4.1	19.6	4.2	19.5	4.1
25-item scale	24.0	4.6	23.8	4.2	24.2	4.9
Baseline Global Assessment Scale score	56.6	6.9	55.8	7.8	57.3	6.2

[a]Log transformation; significant difference between groups (t=–2.13, df=89, p=0.04).

were 30 Hz and 0.3 Hz, respectively, for EEG and EOG, and 90 Hz and 10 Hz for EMG. Paper speed was 10 mm/sec, and sensitivity on the EEG channel was 5.0 μV/mm.

EEG sleep records were scored in 60-second epochs with the use of standard criteria (46). Sleep onset was defined as the first of 10 consecutive minutes of stage 2 or deeper non-REM sleep, interrupted by no more than 2 minutes of stage 1 or wakefulness. REM latency was defined as the interval between sleep onset and the first period of at least 3 consecutive minutes of REM sleep minus intervening wakefulness (47). Phasic REM activity was scored on a 0–8 scale for each minute of sleep. Reliability of the scoring of the sleep variables was excellent (i.e., intraclass correlation coefficients were ≥0.85) and was monitored by monthly reliability checks.

An abnormal EEG sleep profile based on REM latency, sleep efficiency, and REM density was found to discriminate reliably between depressed patients and age-matched healthy control subjects in a previous study (39). The profile was quantified as a discriminant index score, which was computed for each subject with the following equation: $-20.5 + (0.0519 \times \text{REM latency}) - (1.61 \times \text{REM density}) + (0.22 \times \text{sleep efficiency})$ (39). Discriminant index scores of 0 or lower were classified as abnormal. The construct validity of the abnormal classification was supported by the prevalence of these particular sleep disturbances in earlier studies of endogenous depression (48–50), as well as by the association between these variables and hypercortisolism (22, 51–53). The classification showed good test-retest stability (86%) over a 2- to 3-week interval in a study of 22 unmedicated inpatients (39).

When the current study group was classified with the use of this method, 41 subjects (45%) met the criteria for an abnormal sleep profile (i.e., a profile similar to that of depressed inpatients), and 50 subjects (55%) were classified as having a normal sleep profile (i.e., similar to that of healthy control subjects). The percentage of abnormal profiles was virtually identical to the 44% rate observed in an earlier study of an independent group of depressed outpatients (40).

The abnormal/normal sleep profile classification served as the major independent variable in the current study. Table 1 summarizes the demographic and baseline clinical characteristics of the two groups. Patients with abnormal sleep profiles tended to be somewhat older and were more likely to be classified as having the endogenous and/or bipolar II subtype, but these differences were not statistically significant. In fact, only length of current episode differed at the $p \leq 0.05$ level. Exploratory analyses indicated no significant relation whatsoever between length of index episode and any measure of outcome. Therefore, this variable was not covaried in subsequent analyses.

Pretreatment severity of illness was also studied as a main effect because of its potential importance in predicting response to psychotherapy (7). Following the method used in the Treatment of Depression Collaborative Research Program study (41), we classified the illness of patients who scored 19 or lower on the first 17 items of the Hamilton depression scale as "less severe" (N=49) and the illness of patients scoring 20 or higher as "more severe" (N=42).

All patients were treated initially with interpersonal psychotherapy (43). This short-term psychotherapy focuses on difficulties in the patient's current life circumstances and interpersonal relationships. The therapists were experienced social workers or clinical psychologists and were trained to criterion (54) before participating in the research; most had more than 5 years of experience treating depressed outpatients with interpersonal psychotherapy. Although independent assessments of adherence to interpersonal psychotherapy techniques were not carried out, audiotapes of therapy sessions were reviewed by one of us (C.L.C.) in biweekly group supervision.

Acute-phase psychotherapy consisted of up to 16 weekly 45- to 60-minute sessions. Additional sessions were permitted in crisis situations. Patients who were not progressing in therapy could be withdrawn early if there were major clinical concerns. Conversely, partial responders received up to 10 additional weeks of therapy to consolidate a more complete remission.

Patients who did not respond to interpersonal psychotherapy were routinely treated with pharmacotherapy, which was conducted by faculty psychiatrists (D.J.B., C.L.C., A.G.M.). Patients continued to receive interpersonal psychotherapy during pharmacotherapy. During the first 18 months of enrollment, imipramine (150–300 mg/day) was our clinic's drug of choice (N=21). Thereafter, fluoxetine (20–60 mg/day) was used (N=17).

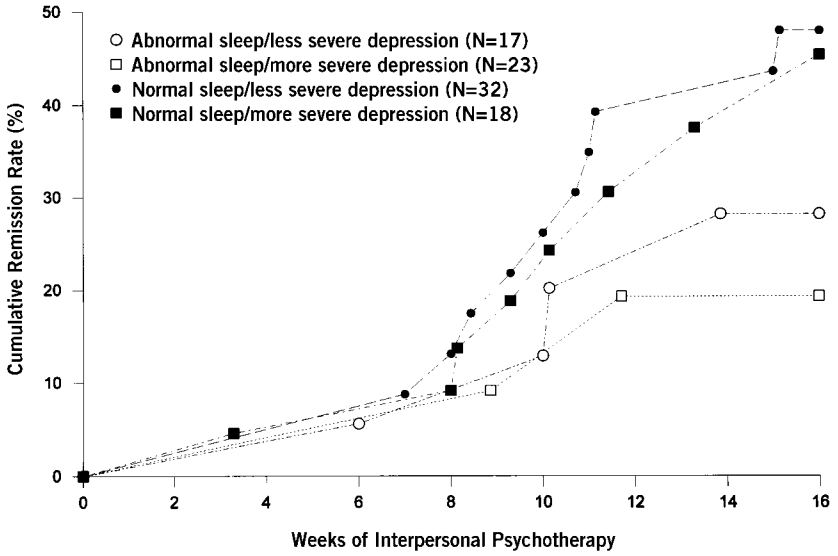
Depressive symptoms were assessed with the Hamilton depression scale at each visit. Remission was defined as 4 consecutive weeks with a 17-item Hamilton depression scale score of 7 or lower. An extended, 25-item version of the Hamilton depression scale (including ratings of hypersomnia, hyperphagia, and weight gain) (55) was used as the continuous outcome measure because of the high prevalence of reversed vegetative symptoms among patients with recurrent depression (56).

Statistical analyses were guided by the intention-to-treat principle; that is, data on all patients who began treatment were included in the analysis. The planned analysis had three steps. First, remission rates following interpersonal psychotherapy and pharmacotherapy were compared by means of chi-square or Fisher's exact probability tests. Second, remission rates over time were compared by means of survival analyses; the cumulative curves were plotted with the use of a

modification of the Kaplan-Meier method (57). This method counts the data of all patients until either the critical outcome (i.e., remission) takes place or the patient is withdrawn from the protocol (i.e., the data are censored) because of attrition or initiation of antidepressant medication. The sleep profile groups were subgrouped by pretreatment severity of illness (more severe/less severe), and statistical significance was tested with the Cox proportional hazard model (57). Third, outcome on the Hamilton depression scale was assessed by using the random effects model with repeated measures for time (58). The random effects model includes all available data points for all subjects who began treatment, without carrying forward endpoint scores. The model studied effects of time (a within-subject effect) and sleep group and severity group (between-subjects effects) and their interactions. For the purposes of this report, assessments at weeks 0, 4, 8, 12, and (if available) 16 were analyzed.

We anticipated a moderate effect size of sleep group (i.e., a between-group difference of about 25% in remission rates) (40). All categorical tests of a priori hypotheses were therefore made with one-sided tests in order to maximize statistical power (59). With cell numbers of 41 and 49, the power to detect a difference of this magnitude (e.g., 60% versus 35%) with a 2×2 chi-square test was 0.77 for a one-sided test (alpha=0.05) (59). The Wald Z score transformation was used to calculate one-sided probabilities for the log-rank chi-square statistic derived from the survival analysis.

FIGURE 1. Cumulative Remission Rates of Patients With Major Depression, Stratified by Sleep Profile and Severity of Illness, Treated With Interpersonal Psychotherapy



RESULTS

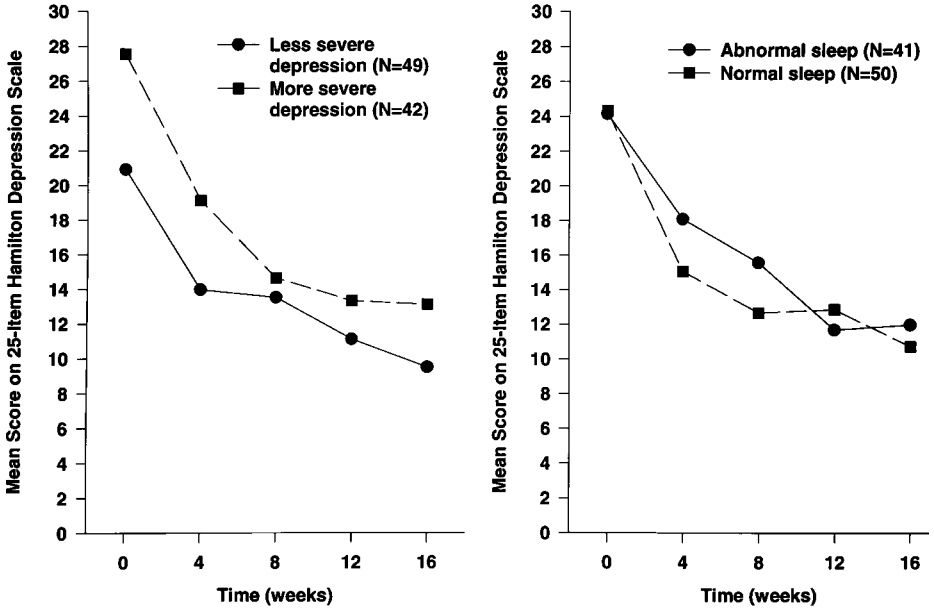
The patients received a mean of 12.6 sessions (SD= 7.6) of interpersonal psychotherapy, and 45 patients (49%) completed 12 or more sessions of therapy. Among those who did not complete 12 weeks of interpersonal psychotherapy alone, three dropped out for personal reasons, three were withdrawn because of noncompliance, one was withdrawn when a concomitant diagnosis of sleep apnea was confirmed, 20 were withdrawn early because they did not respond to treatment, and 19 terminated early after achieving remission.

Forty-four patients (48%) achieved remission with interpersonal psychotherapy alone; these included 12 (46%) of the 26 men and 32 (49%) of the 65 women. Eighteen (43%) of the 42 patients in the more severely ill group had remissions, compared with 26 (53%) of the 49 in the less severely ill group (p=0.22, Fisher's exact probability test). By contrast, remission rates differed significantly in the EEG sleep groups: 15 patients (37%) with abnormal pretreatment sleep profiles experienced remission, compared with 29 patients (58%) in the normal sleep group (p=0.03, Fisher's exact probability test).

Figure 1 depicts the cumulative remission rates in the normal and abnormal sleep groups, stratified by severity subgroup. As was the case with the simple categorical comparison, there was a modest but statistically significant effect of sleep group (Wald Z=1.68, p<0.05). Furthermore, attrition from acute treatment with interpersonal psychotherapy alone was nonrandom: the data of significantly more patients in the abnormal sleep group were censored from the life table analysis before remission (χ^2=5.1, df=1, p=0.01). Neither severity (p=0.56) nor the severity-by-sleep-group interaction (p=0.63) contributed significantly in the Cox proportional hazard model analysis. Median times to remission could not be compared because of the low remission rate in the abnormal sleep group.

In the random effects model analysis of Hamilton depression scale scores, the main effect of time was significant (F=76.64, df=4, 326, p<0.0001) and the main effect of severity was significant (F=14.12, df=1, 87, p=0.0003), whereas the main effect of sleep group was not (F=1.36, df=1, 87, p=0.25). Importantly, both the severity-by-time interaction and the sleep-group-by-time interaction were significant (F=3.53, df=4, 326, p<0.008, and F=2.43, df= 4, 326, p<0.05, respectively). Figure 2 illustrates these interactions. In the left panel, the severity-by-time interaction reflects a more rapid decline of Hamilton depression scale scores among the more severely depressed patients. Interpretation of this finding is compromised, however, by the possibility of regression to the mean (i.e., the higher scores of the more severely ill group may simply fall faster). The right panel illustrates that the sleep-group-by-time interaction was principally a function of the poorer outcome of the abnormal sleep profile group during the first 8 weeks of therapy. Neither the interaction term for sleep group by severity group nor the interaction term for sleep group by severity group by time was significant (F=0.17, df=1, 87, p=0.68, and F=0.49, df=4, 326, p=0.74). Of note, patients in the abnormal sleep group who completed at least 12 weeks of interpersonal psychotherapy ended treatment with Hamilton depression scale scores similar to those in the normal sleep profile group (figure 2, right panel).

FIGURE 2. Mean Scores on the Hamilton Depression Scale (25-item Version) of Patients With Major Depression, Stratified by Sleep Profile and Severity of Illness, Treated With Interpersonal Psychotherapy[a]



[a]Random effects model analysis. Left panel illustrates the severity-by-time interaction. Right panel illustrates the sleep-group-by-time interaction.

Thirty-seven of the 47 patients who did not respond to interpersonal psychotherapy were treated with pharmacotherapy. Among the 10 other nonresponders to interpersonal psychotherapy, seven had withdrawn from the study and three declined pharmacotherapy. Response to pharmacotherapy was similar in the abnormal and normal sleep groups (remission rates: abnormal sleep group, 75% [N=15 of 20]; normal sleep group, 71% [N=12 of 17]; χ^2=0.01, df=1, p=0.94). When outcomes were compared across treatment phases, however, the abnormal sleep group had a significantly higher remission rate when treated with the combination of pharmacotherapy and interpersonal psychotherapy (75%) than when treated with interpersonal psychotherapy alone (37%) (χ^2=7.9, df=1, p< 0.001), whereas outcomes of the two treatments were more comparable in the normal sleep group (71% versus 58%; χ^2=0.8, df=1, p=0.36).

DISCUSSION

These findings replicate and extend our group's initial report (40) documenting poorer response to cognitive behavior therapy among patients with abnormal EEG sleep profiles. When the two studies are compared, the remission rates after psychotherapy of patients with abnormal sleep profiles (45% and 37%) are quite similar. The effect sizes observed in these two studies (i.e., 21% differences in remission rates) are both clinically meaningful and similar to the average drug/placebo difference observed in controlled pharmacotherapy studies of major depressive disorder (4). Importantly, we also found that patients with abnormal sleep profiles did not have inherently poor prognoses: 75% of the patients who did not respond to interpersonal psychotherapy had remissions following the addition of pharmacotherapy.

There was no evidence that pretreatment severity of illness adversely affected response to interpersonal psychotherapy. The literature pertaining to the relation between severity of symptoms and response to psychotherapy shows mixed results (60), and several other groups besides ours have also failed to find such a relationship (61, 62). Of particular interest are the findings of the Treatment of Depression Collaborative Research Program study (41), in which patients with Hamilton depression scale scores above 20 responded as well to interpersonal psychotherapy as those with less severe depressive episodes.

The current study has several potentially important implications. First, our findings are consistent with the traditional view that more "biologically disturbed" depressive episodes are less responsive to psychotherapy (3, 5, 9). Conversely, among the patients who did not respond to interpersonal psychotherapy, pharmacotherapy was equally effective for those with abnormal and those with normal sleep profiles.

Second, as in our earlier study (40), the relation between EEG sleep abnormality and response to therapy was not a simple epiphenomenon of severity of symptoms. This may help to explain why studies using clinical assessments of severity or endogenous symptoms have not consistently documented differences in response to psychotherapy or pharmacotherapy (6, 7). Specifically, it may be that only the subgroup of depressed patients who exhibit objective signs of neurobiological dysfunction are less responsive to psychotherapy. In this regard, poorer response to psychotherapy among depressed patients has also been associated with nonsuppression of cortisol on the DST or elevated urinary free cortisol concentrations (16–19).

Third, it has been hypothesized that the abnormal EEG sleep profile reflects a state of pathologically increased CNS arousal (50). This state may be the result of high levels of corticotropin-releasing hormone, relatively increased cholinergic activity, and/or decreased inhibitory serotonergic neurotransmission (11). Consistent with the nocturnal hyperarousal hypothesis,

preliminary studies of glucose metabolism during the first non-REM period show that depressed patients have *higher* metabolic rates than nondepressed control subjects in almost all brain areas, including the prefrontal cortex (63). By contrast, functional imaging studies in depressed patients who are awake have shown decreased glucose metabolism in the anterolateral prefrontal cortex, particularly in the left hemisphere (64, 65).

The relation between disturbances of sleep neurophysiology and impaired waking prefrontal cortical function may hinge on neural circuits that link the pontine cholinergic nuclei that trigger the onset of REM sleep with the thalamus and ascending thalamocortical pathways (66). Regions of the thalamus involved in generation of slow wave sleep also form circuits with the prefrontal cortex (66, 67). Thus, abnormally increased "drive" from the brainstem during sleep may cause a compensatory or pathologic dysregulation of prefrontal cortical activity. Such dysfunction, in turn, may account for the depressed patient's problems in using abstraction or complex problem-solving skills in therapy (40). Other related neurophysiological alterations, including the cumulative effects of poor sleep (67), cognitive deficits mediated by hypercortisolism (19, 68), blunting of noradrenergic and dopaminergic mechanisms involved in hedonic capacity (69, 70), and persistently intense dysphoric affects associated with increased phasic REM sleep (71), may also contribute to the inability of some depressed people to use therapy successfully (40). Patients manifesting such disturbances may respond preferentially to pharmacotherapy or ECT because of the more powerful or direct effects of these treatments on relevant neurophysiological processes, including REM suppression, enhancement of serotonergic neurotransmission, and stabilization of HPA activity (11, 72).

Despite such interesting implications, the immediate clinical utility of EEG sleep studies for prediction of differential response to treatment is limited by the expense and inconvenience of all-night polysomnographic studies. If our hypothesis about impaired neural systems is correct, more finely tuned clinical assessments of attention span, working memory, mood reactivity, and hedonic capacity may provide a more feasible way to predict responsiveness to psychotherapy.

Other limitations of the current study include the lack of parallel comparison groups treated with attention/placebo and pharmacological interventions and the exclusion of patients with serious comorbidity. The former precludes an assessment of interpersonal psychotherapy's efficacy per se, whereas the latter limits generalizability to unselected populations. It could also be argued that a number of the nonresponders to interpersonal psychotherapy received suboptimal trials of therapy. For example, 44% of the nonresponders attended fewer than 12 sessions of therapy, and the integrity of the interpersonal psychotherapy sessions was not confirmed by an independent expert reviewer. Consistent with this suggestion, the response of the abnormal and normal sleep groups did not differ significantly with respect to the subset of patients who completed at least 12 weeks of interpersonal psychotherapy.

In summary, our findings support a traditional model of differential therapeutics for the depressive disorders that has been difficult to confirm with empirical data (7, 60). These findings suggest that a neurobiological "boundary" may delimit outpatients' response to psychotherapy but not to pharmacotherapy. Concomitant studies of HPA activity may help to define this boundary further (16–19). Identifying waking clinical correlates of these boundary markers represents a major challenge for future research.

REFERENCES

1. Kraepelin E: Manic-Depressive Insanity and Paranoia. Translated by Barclay RM, edited by Robertson GM. Edinburgh, E & S Livingstone, 1921
2. Gillespie RD: The clinical differentiation of types of depression. Guys Hosp Rep 1929; 79:872–882
3. Free ML, Oei TPS: Biological and psychological processes in the treatment and maintenance of depression. Clin Psychol Rev 1989; 9:653–688
4. Clinical Practice Guideline: Depression in Primary Care, vol 1: Detection and Diagnosis. Rockville, Md, US Department of Health and Human Services, 1993
5. American Psychiatric Association: Practice Guideline for Major Depressive Disorder in Adults. Am J Psychiatry 1993; 150(April suppl)
6. Jarrett RB, Rush AJ: Short-term psychotherapy of depressive disorders: current status and future directions. Psychiatry 1994; 57: 115–132
7. Thase ME: Reeducative psychotherapies, in Treatments of Psychiatric Disorders, 2nd ed, vol 1. Edited by Gabbard GO. Washington, DC, American Psychiatric Press, 1995, pp 1169–1204
8. Zimmerman M, Spitzer RL: Melancholia: from DSM-III to DSM-III-R. Am J Psychiatry 1989; 146:20–28
9. Rush AJ, Weissenburger JE: Melancholic symptom features and DSM-IV. Am J Psychiatry 1994; 151:489–498
10. Parker G, Hadzi-Pavlovic D, Boyce P, Wilhelm K, Brodaty H, Mitchell P, Hickie I, Eyers K: Classifying depression by mental state signs. Br J Psychiatry 1990; 157:55–65
11. Thase ME, Howland R: Biological processes in depression: updated review and integration, in Handbook of Depression. Edited by Beckham EE, Leber WR. New York, Guilford Press, 1995, pp 213–279
12. Parker G, Hadzi-Pavlovic D, Boyce P: Endogenous depression as a construct: a quantitative analysis of the literature and a study of clinician judgements. Aust NZ J Psychiatry 1989; 23:357–368
13. Carroll BJ: The dexamethasone suppression test for melancholia. Br J Psychiatry 1982; 140:292–304
14. Kupfer DJ, Thase ME: Laboratory studies and validity of psychiatric diagnosis: has there been progress? in Validity of Psychiatric Diagnosis. Edited by Robins LN, Barrett JE. New York, Raven Press, 1989, pp 223–242
15. Ribeiro SCM, Tandon R, Grunhaus L, Greden JF: The DST as a predictor of outcome in depression: a meta-analysis. Am J Psychiatry 1993; 150:1618–1629
16. Robbins DR, Alessi NE, Colfer MV: Treatment of adolescents with major depression: implications of the DST and melancholia clinical subtype. J Affect Disord 1989; 17:99–104
17. Corbishley M, Beutler L, Quan S, Bamford C, Meredith K, Scogin F: Rapid eye movement density and latency and dexamethasone suppression as predictors of treatment response in depressed older adults. Curr Ther Res 1990; 47:846–859
18. McKnight DL, Nelson-Gray RO, Barnhill J: Dexamethasone suppression test and response to cognitive therapy and antidepressant medications. Behavior Therapy 1992; 1:99–111

19. Thase ME, Dubé S, Bowler K, Howland RH, Myers JE, Friedman E, Jarrett DB: Hypothalamic-pituitary-adrenocortical activity and response to cognitive behavior therapy in unmedicated, hospitalized depressed patients. Am J Psychiatry 1996; 153:886–891
20. Benca RM, Obermeyer WH, Thisted RA, Gillin JC: Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry 1992; 4:651–668
21. Buysse DJ, Kupfer DJ: Sleep disorders in depressive disorders, in Biology of Depressive Disorders, Part A: A Systems Perspective. Edited by Mann JJ, Kupfer DJ. New York, Plenum, 1993, pp 123–154
22. Feinberg M, Carroll BJ: Biological "markers" for endogenous depression: effect of age, severity of illness, weight loss, and polarity. Arch Gen Psychiatry 1984; 41:1080–1085
23. Giles DE, Schlesser MA, Rush AJ, Orsulak PJ, Fulton CL, Roffwarg HP: Polysomnographic findings and dexamethasone nonsuppression in depression: a replication and extension. Biol Psychiatry 1987; 22:872–882
24. Akiskal HS, Rosenthal TL, Haykal RF, Lemmi H, Rosenthal RH, Scott-Strauss A: Characterological depressions: clinical and sleep EEG findings separating subaffective dysthymias from character spectrum disorders. Arch Gen Psychiatry 1980; 37: 777–783
25. Svendson K, Christensen PG: Duration of REM sleep latency as predictor of effect of antidepressant therapy. Acta Psychiatr Scand 1981; 64:238–243
26. Rush AJ, Erman MK, Schlesser MA, Roffwarg HP, Vasavada N, Khatami M, Fairchild C, Giles DE: Alprazolam vs amitriptyline in depressions with reduced REM latencies. Arch Gen Psychiatry 1985; 42:1154–1159
27. Rush AJ, Giles DE, Jarrett RB, Feldman-Koffler F, Debus JR, Weissenburger J, Orsulak PJ, Roffwarg HP: Reduced REM latency predicts response to tricyclic medication in depressed outpatients. Biol Psychiatry 1989; 26:61–72
28. Zammit G, Rosenbaum A, Stokes P, Davis J, Zorick F, Roth T: Biological differences in endogenous depressive placebo responders versus nonresponders: dexamethasone suppression test and sleep EEG data. Biol Psychiatry 1988; 24:97–101
29. Heiligenstein JH, Faries DE, Rush AJ, Andersen JS, Pande AC, Roffwarg HP, Dunner D, Gillin JC, James SP, Lahmeyer H, Zajacka J, Tollefson GD, Gardner DM: Latency to rapid eye movement sleep as a predictor of treatment response to fluoxetine and placebo in nonpsychotic depressed outpatients. Psychiatry Res 1994; 52:327–339
30. Giles DE, Rush AJ, Jarrett RB, Roffwarg HP: Reduced rapid eye movement latency: a predictor of recurrence in depression. Neuropsychopharmacology 1987; 1:33–39
31. Buysse D, Kupfer DJ, Frank E, Monk T, Rittenour A, Ehlers CL: Electroencephalographic sleep studies in depressed patients treated with psychotherapy, I: baseline studies in responders and nonresponders. Psychiatry Res 1992; 42:13–26
32. Jarrett RB, Rush AJ, Khatami M, Roffwarg HP: Does the pretreatment polysomnogram predict response to cognitive therapy in depression outpatients? a preliminary report. Psychiatry Res 1990; 33:285–299
33. Simons AD, Thase ME: Biological markers, treatment outcome, and 1-year follow-up in endogenous depression: electroencephalographic sleep studies and response to cognitive therapy. J Consult Clin Psychol 1992; 60:392–401
34. Thase ME, Bowler K, Harden T: Cognitive behavior therapy of endogenous depression, part 2: preliminary findings in 16 unmedicated inpatients. Behavior Therapy 1991; 22:469–477
35. Thase ME, Reynolds CF III, Frank E, Jennings JR, Nofzinger E, Fasiczka AL, Garamoni GL, Kupfer DJ: Polysomnographic studies of unmedicated depressed men before and after cognitive behavior therapy. Am J Psychiatry 1994; 151:1615–1622
36. Thase ME, Simons AD: The applied use of psychotherapy in the study of the psychobiology of depression. J Psychotherapy Practice and Res 1992; 1:72–80
37. Giles DE, Kupfer DJ, Roffwarg HP, Rush AJ, Biggs MM, Etzel BA: Polysomnographic parameters in first-degree relatives of unipolar probands. Psychiatry Res 1989; 27:127–136
38. Kupfer DJ, Ehlers CL: Two roads to REM latency. Arch Gen Psychiatry 1989; 46:945–948
39. Thase ME, Kupfer DJ, Fasiczka AJ, Buysse DJ, Simons AD, Frank E: Validation of an abnormal EEG sleep profile characteristic of major depression. Biol Psychiatry (in press)
40. Thase ME, Simons AD, Reynolds CF III: Abnormal electroencephalographic sleep profiles in major depressions: association with response to cognitive behavior therapy. Arch Gen Psychiatry 1996; 53:99–108
41. Elkin I, Shea MT, Watkins JT, Imber SD, Sotsky SM, Collins JF, Glass DR, Pilkonis PA, Leber WR, Docherty JP, Fiester SJ, Parloff MB: National Institute of Mental Health Treatment of Depression Collaborative Research Program: general effectiveness of treatments. Arch Gen Psychiatry 1989; 46:971–982
42. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
43. Klerman GL, Weissman MM, Rounsaville BJ, Chevron ES: Interpersonal Psychotherapy of Depression. New York, Basic Books, 1984
44. Endicott J, Spitzer RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978; 35:837–844
45. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 1978; 35:773–782
46. Rechtschaffen A, Kales A (eds): A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects: NIH Publication 204. Bethesda, Md, Public Health Service, National Institutes of Health, 1968
47. Reynolds CF, Taska LS, Jarrett DB, Coble PA, Kupfer DJ: REM latency in depression: is there one best definition? Biol Psychiatry 1983; 18:849–863
48. Gillin JC, Duncan W, Pettigrew KD, Frankel BL, Snyder F: Successful separation of depressed, normal, and insomniac subjects by EEG sleep data. Arch Gen Psychiatry 1979; 36:85–90
49. Feinberg M, Gillin JC, Carroll BJ, Greden JF, Zis AP: EEG studies of sleep in the diagnosis of depression. Biol Psychiatry 1982; 17:305–316
50. Thase ME, Kupfer DJ, Ulrich RF: Electroencephalographic sleep in psychotic depression: a valid subtype? Arch Gen Psychiatry 1986; 43:886–893
51. Rush AJ, Giles DE, Roffwarg HP, Parker CR: Sleep EEG and dexamethasone suppression test findings in outpatients with unipolar major depressive disorders. Biol Psychiatry 1982; 17: 327–341
52. Mendlewicz J, Kerhofs M, Hoffman G, Linkowski P: Dexamethasone suppression test and REM sleep in patients with major depressive disorder. Br J Psychiatry 1984; 145:383–388
53. Poland RE, McCracken JT, Lutchmansingh P, Tondo L: Relationship between REM sleep latency and nocturnal cortisol concentrations in depressed patients. J Sleep Res 1992; 1:54–57
54. Rounsaville BJ, Chevron ES, Weissman MM: Specification of techniques in interpersonal psychotherapy, in Psychotherapy Research. Edited by Williams JBW, Spitzer RL. New York, Guilford Press, 1984, pp 160–172
55. Thase ME, Frank E, Mallinger A, Hamer T, Kupfer DJ: Treatment of imipramine-resistant recurrent depression, III: efficacy of monoamine oxidase inhibitors. J Clin Psychiatry 1992; 53:5–11
56. Thase ME, Carpenter L, Kupfer DJ, Frank E: Clinical significance of reversed vegetative subtypes of recurrent major depression. Psychopharmacol Bull 1991; 27:17–22
57. Cox DR, Oakes D: Analysis of Survival Data. London, Chapman & Hall, 1984
58. Gibbons RD, Hedeker D, Elkin I, Waternaux C, Kraemer HC, Greenhouse JB, Shea T, Imber SD, Sotsky SM, Watkins JT: Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Arch Gen Psychiatry 1993; 50:739–750
59. Kraemer HC, Thiemann S: How Many Subjects? Statistical Power Analysis in Research. Newbury Park, Calif, Sage Publications, 1987
60. Persons JB, Thase ME, Crits-Christoph P: The role of psychotherapy in the treatment of depression. Arch Gen Psychiatry 1996; 53:283–290

61. Hollon SD, DeRubeis RJ, Evans MD, Wiemer MJ, Garvey MJ, Grove WM, Tuason VB: Cognitive therapy and pharmacotherapy of depression: singly and in combination. Arch Gen Psychiatry 1992; 49:774–781
62. McLean PD, Taylor S: Severity of unipolar depression and choice of treatment. Behav Res Ther 1992; 30:443–451
63. Gillin JC, Wu J, Buchsbaum M, Ho A, Hong C, Valladares Neto DC, Bunney W: S-125-538 cerebral glucose metabolism in normal controls and depressed patients during nonREM sleep and after sleep deprivation. Neuropsychopharmacology 1994; 10:15–22
64. Baxter JR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM: Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry 1989; 46:243–250
65. George MS, Ketter TA, Post RM: Prefrontal cortex dysfunction in clinical depression. Depression 1994; 2:59–72
66. Steriade M: Sleep oscillations and their blockage by activating systems. J Psychiatr Neurosci 1994; 19:354–358
67. Horne JA: Human sleep, sleep loss and behavior: implications for the prefrontal cortex and psychiatric disorder. Br J Psychiatry 1993; 162:192–205
68. Reus VI: Hormonal mediation in the memory disorder in depression. Drug Development Res 1985; 4:489–500
69. Wilner P, Golembiowski K, Klimek V, Muscat R: Changes in mesolimbic dopamine may explain stress-induced anhedonia. Psychobiology 1991; 19:79–84
70. Weiss JM: Stress-induced depression: critical neurochemical and electrophysiological changes, in Neurobiology of Learning, Emotion, and Affect. Edited by Madden J. New York, Raven Press, 1991, pp 123–154
71. Nofzinger EA, Schwartz RM, Reynolds CF III, Thase ME, Jennings RJ, Fasiczka AL, Garamoni GL, Kupfer DJ: Affect intensity and phasic REM sleep in depressed men before and after treatment with cognitive behavior therapy. J Consult Clin Psychiatry 1994; 62:83–91
72. Barden N, Reul JM, Holsboer F: Do antidepressants stabilize mood through actions on the hypothalamic-pituitary-adrenocortical system? Trends Neurosci 1995; 18:6–11