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REM Latency Distribution in Major Depression: Clinical Characteristics Associated with Sleep Onset REM Periods

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In a sample of 92 inpatients with major depression, REM latency showed a unimodal, rather than bimodal, distribution, with peak frequency between 50-59 min (on each of 4 consecutive nights). A total of 20 patients (21.6%) exhibited a sleep onset REM period (SOREMP-10) i.e., REM latency ≤10 min, during at least 1 of the 4 nights; an additional 11 patients (12%) showed REM latencies of 11-20 min on at least one night. SOREMP-10 positive patients were older both at the time of study ($p < 0.01$) and at the age of onset of depressive illness ($p < .01$) than the rest of the sample. They also showed greater sleep continuity disturbances, while patients with at least one SOREMP-20, i.e., REM latency ≤20 min, exhibited higher REM percentage ($p \leq 0.05$) and a higher first-period density ($p < 0.05$) than the remaining patients. No other clinical or polysomnographic correlates of SOREMP positivity were noted with regard to gender, RDC subtypes, severity of illness, or clinical response to tricyclic antidepressants. The unimodal distribution of REM latency, as well as the absence of a relationship between SOREMP positivity and severity of de-

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pression or therapeutic outcome, may result from the low representation of psychotic depressives in this sample (n = 6), who might constitute a qualitatively different subgroup.

INTRODUCTION

Among the abnormalities of sleep in major depressive illness, shortened REM latency appears to be the most common feature (for review, see Kupfer, 1976; Kupfer *et al.*, 1978). Recently, Schulz *et al.* (1979) suggested a bimodal distribution of REM latency in endogenous depressives, with peaks just after sleep onset (sleep onset REM periods or SOREMPs[4]) and 40-60 min later. The results of this study, which included six patients with a total of 90 recording nights, were largely confirmed in a more extensive study by Coble *et al.* (1981) of 22 patients during a total of 737 nights. SOREMPs-10 were present during 18% of the nights and SOREMPs-20 during 22.5% of the nights; 36.4% of patients exhibited 1 to 9 nights with SOREMPs-20 and 40.9%, 10 or more SOREMPs-20. Interestingly, the subgroup of psychotic depressives exhibited the largest number of SOREMPs: 36.3% of the nights with SOREMPs-10.

The SOREMP phenomenon has been used as an indicator of narcolepsy (Rechtschaffen *et al.*, 1963). Montplaisir (1976) found a frequency of 49% of REM latencies shorter than 15 min in nocturnal recordings of narcoleptics, increasing to 66% among patients who were permitted to nap during the day. He also found a clear bimodal distribution of REM latencies, with SOREMPs falling between 0 and 15 min and other REM latencies longer than 45 min. The similarities between the sleep of depressives and narcoleptics led Reynolds *et al.* (1983) to compare EEG sleep findings in the two groups. This study clearly showed a higher occurrence of SOREMPs-10 in narcoleptics than in age-matched depressives (48% *vs.* 4% of patients), but was performed in nonpsychotic unipolar outpatients, whereas all studies demonstrating SOREMPs in depressives have been performed in inpatients with a higher level of severity and a greater likelihood of psychotic features.

The clinical correlates of depressive patients exhibiting SOREMPs have been insufficiently studied. Coble *et al.* (1981) suggested that the presence of SOREMPs generally predicted an inadequate response to tricyclic antidepressants and the need to use combined pharmacotherapy (tricyclics plus neuroleptics). Supporting this hypothesis, Kupfer *et al.* (1983a) found that delusional depressives, nonresponders to either amitriptyline or combined therapy (and

[4]In this study, we use "SOREMP-10" for REM latency ≤10 min and "SOREMP-20" for REM latency ≤20 min. Therefore, SOREMPs 10 are included in the SOREMPs-20.

thus requiring ECT), exhibited a much shorter REM latency than the pharmacological treatment responders (18.6 *vs.* 65.3 min). Schultz and Tetzlaff (1982) found that their depressives exhibiting SOREMPs were significantly more depressed.

This last finding confirms the negative correlation reported between REM latency and the severity of depressive illness (Kupfer and Foster, 1972; Spiker *et al.*, 1978). While severe depressives may exhibit a mean REM latency as short as 10 min (Kupfer and Foster, 1975), extremely short REM latencies seem also particularly frequent in delusional depressives (Kupfer *et al.*, 1983a), a finding also noted by Snyder (1972) who stated that they "appear to be almost pathognomonic of psychotic depressives."

On the other hand REM latency also shows a marked age-related decrease in depressives (Ulrich *et al.*, 1980; Gillin *et al.*, 1981; Kupfer *et al.*, 1982), with a mean value as low as 23.9 min in the group of inpatients from 51 to 60 years of age. Taken together, these data suggest that SOREMP-positive depressives could differ from SOREMP-negative depressives by being older and/or showing greater severity of illness, presence of psychotic features, and/or poor response to standard antidepressant treatment. In order to address these issues further, therefore, the current study aimed: (i) to attempt replication of earlier reports of bimodal distribution in REM latency; and (ii) to reassess possible correlates of the SOREMP phenomenon in a large sample of depressive inpatients. We asked whether, in fact, these patients could represent a very specific subgroup of depressives: demographically, clinically, biochemically, and therapeutically.

SUBJECTS AND METHOD

Sample and Procedure

Ninety-two inpatients on the Clinical Research Unit of Western Psychiatric Institute and Clinic were included in the study. These patients represented consecutive admissions who met Research Diagnostic Criteria for a major depressive disorder (Spitzer *et al.*, 1978). At the time of admission, in addition to a clinical interview and physical examination, collateral information was obtained from patient's families and from case records of previous hospitalizations. During a 2-week drug-free period, patients underwent a series of routine laboratory tests, including complete blood count, chemistry screen, electrocardiogram, urine analysis, thyroid function tests, and a 16-channel 10/20 EEG, as well as any other tests indicated by their history or physical examination. In addition, all patients were observed for clinical evidence of daytime sleep attacks and cataplexy, to exclude subjects with possible narcolepsy. After the drug-free period, each patient's psychiatrist filled out the lifetime version of the *Schedule for Affective Disorders and Schizophrenia* (SADS-L) (Spitzer and Endicott, 1977), on

the basis of best available information, obtained from the initial interview, case records, collateral data from relatives, observation on the Unit, and a second interview with the patient. If the severity of depression remained sufficiently high at the end of the drug-free period (a minimum score of 30 on the 17-item Hamilton Depression Scale, using the sum of two raters), patients then entered the protocol.

The protocol consisted of four consecutive all-night sleep EEG recordings. Subjects slept in their own rooms on the Clinical Research Unit while recordings were made in the Sleep Evaluation Center, using the Grass Model 78-B polygraph. Nightly recordings of EEG (C4-A1), electrooculogram, and chin electromyogram were scored manually by research assistants blind to diagnosis, according to the criteria of Rechtschaffen and Kales (1968). In addition to the standard scoring, records were also scored for REM activity on an analog scale from 0 to 8 for each minute of REM sleep, as described previously (Kupfer *et al.*, 1974). Sleep onset was defined by the 1st min of Stage 2 sleep followed by at least 10 min of Stage 2 sleep, interrupted by no more than 2 min of awake or Stage 1. REM latency was defined as the time between sleep onset and first REM period (3 min) minus any intervening wake time. Patients were treated with either amitriptyline (n = 73) or nortriptyline (n = 19) in double-blind conditions, with a dosage of nortriptyline half that of amitriptyline. They received four identical study capsules daily during the protocol. The first 5 days represented a placebo period. They then received, in stepwise fashion, 50/25 mg of amitriptyline/nortriptyline for 2 nights, 100/50 mg daily (50/25 mg at 5 PM and 9 PM) for the next 3 days, a 4-day period of 150/75 mg daily (50/25 mg at 1 PM, 5 PM, and 9 PM), and finally a 14-day period at a dose level of 200/100 mg daily (50/25 mg qid). The Hamilton Depression, Brief Psychiatric (BPRS), Raskin, and Beck Rating Scales were used weekly throughout the study. The patients were defined as treatment responders (n = 65) if their final Hamilton score was 19 or less and nonresponders (n = 27) if their final Hamilton score was 20 or higher (two-rater sum).

The study included 31 male and 61 female patients, with an age range of 18 to 69 (mean = 36.5 ± 12.6). The characteristics of the sample according to the RDC subtypes of major depressive disorder are displayed in Table II.

Data Analysis

The distribution of REM latency values during each of the four recording nights was assessed using the chi-square statistic. To examine possible correlates of SOREMP positivity, the sample was divided into three groups: (i) patients exhibiting at least one SOREMP-10 during the 4 consecutive recording nights (n = 20); (ii) patients exhibiting no SOREMP-10 but at least one REM latency between 11 and 20 min (n = 11); and (iii) patients without any REM latency

of 20 min or less during the 4 recording nights ($n = 61$). This categorization was made to ensure that clinical characteristics of patients exhibiting SOREMPs-20 did not depend only on patients with SOREMP-10. The demographic features, clinical features, clinical response to antidepressant therapy, and the RDC characteristics of each group were then analyzed using the chi-square statistic. Additional clinical characteristics (e.g., age, baseline and final rating scale scores, duration of episode, number of episodes, age at first onset) were compared using univariate analysis of variance (ANOVA). These variables were transformed via the natural logarithm in order to normalize distributions. To test for differences in the hand-scored sleep data among the three groups, a two-factor analysis of variance (using group and night) with repeated measures (the 4 recording nights) was run for each variable. A priori nonorthogonal contrasts were then made using Dunn's multiple comparison procedure.

RESULTS

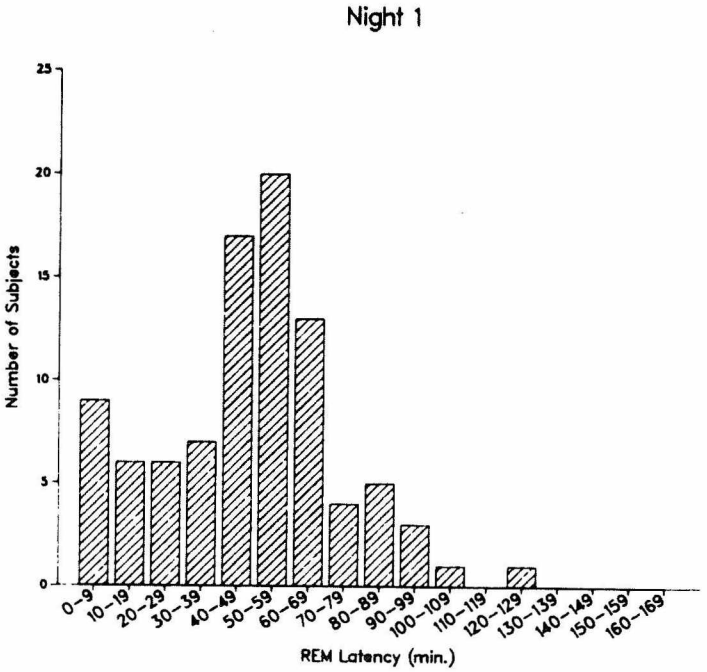
REM Latency Distribution

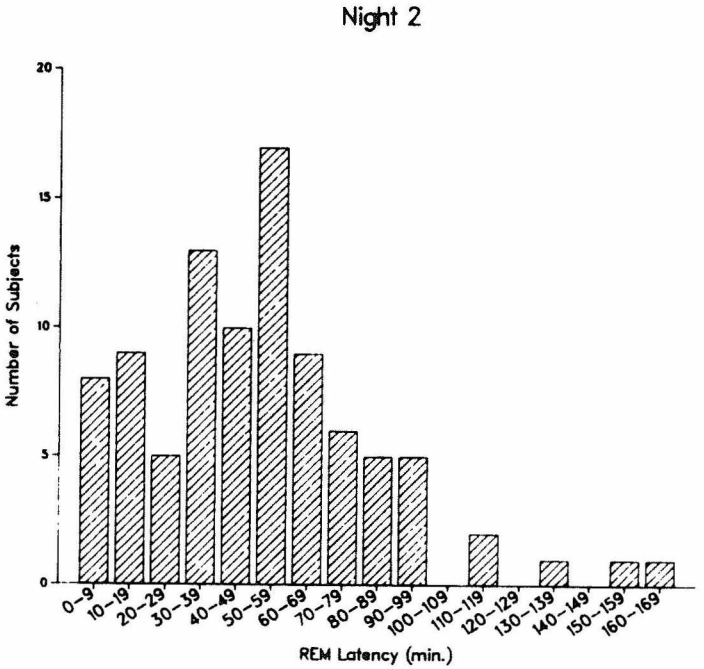
When the distribution of REM latency during each individual recording night and during all 4 nights (pooled) was examined (Figs. 1-2), a unimodal and continuous, rather than bimodal and discontinuous, distribution was evident. Moreover, during each of the 4 nights, no statistical difference in number of REM latency values falling between 0-19 min, and 20-39 min was found: for Night 1, 15 *vs.* 13 ($\chi^2 = .14$, ns); for Night 2, 17 *vs.* 18 ($\chi^2 = 0.11$, ns); for Night 3, 16 *vs.* 20 ($\chi^2 = .44$, ns); and for Night 4, 11 *vs.* 16 ($\chi^2 = 0.93$, ns). During each of the 4 recording nights, peak frequency of REM latency values fell between 50-59 min.

SOREMPs-10 were present during a total of 35 nights (9.5%) and SOREMPs-20 during a total of 62 nights (16.8%). The distribution of SOREMPs by night of occurrence is displayed in Table I, as are the numbers of patients with SOREMPs.

Clinical Correlates of SOREMPs

When the comparative frequencies of demographical and clinical characteristics (gender, clinical response, and RDC subtype) in each of the three groups were analyzed (Table II), no statistically significant differences were found. However, when compared with the remainder of the sample ($n = 72$), the SOREMP-10-positive group ($n = 20$) showed a trend toward an excess of bipolar II depressives (15% *vs.* 2.8%, $p = 0.07$, Fisher's exact test). Also pa-


Night 1
Number of Subjects
25
20
15
10
5
0
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
90-99
100-109
110-119
120-129
130-139
140-149
150-159
160-169
REM Latency (min.)


Night 2
Number of Subjects
20
15
10
5
0
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
90-99
100-109
110-119
120-129
130-139
140-149
150-159
160-169
REM Latency (min.)

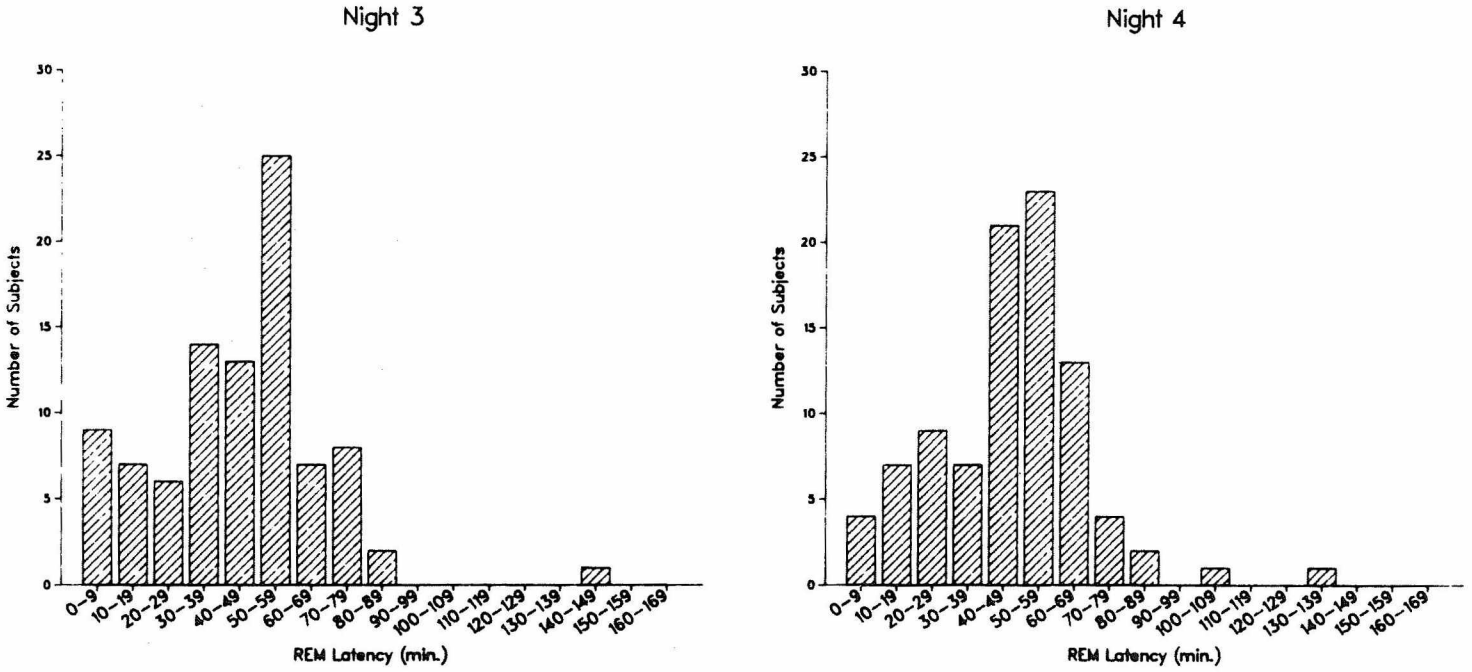


Fig. 1. Distribution of REM latency values in 92 depressives during each of four consecutive recording nights (n = 368 nights).

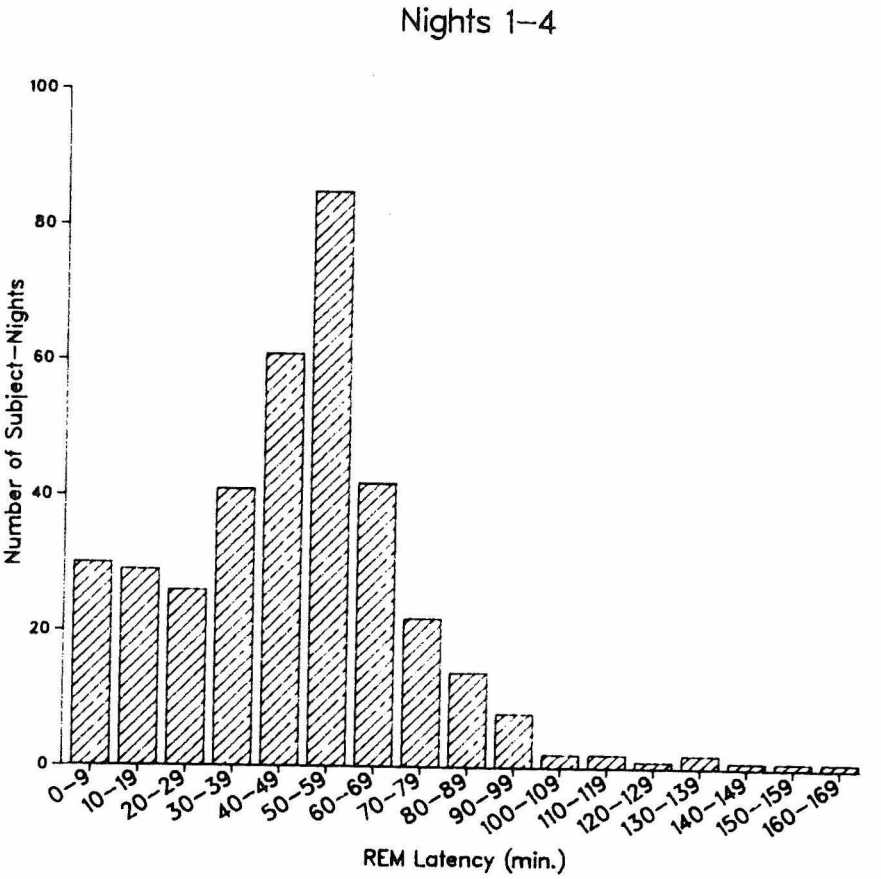


Fig. 2. Distribution of REM latency values in 92 depressives recorded during four consecutive nights (n = 368 nights).

tients with a SOREMP-10 on at least one night were significantly older at the time of the study ($p < 0.01$) and at the age of onset of depressive illness ($p < 0.01$) (Table III).

With regard to sleep characteristics (Table IV), patients with SOREMPs-10 (n = 20) had longer sleep latency ($p < 0.05$), spent less time asleep ($p < 0.01$), and had lower sleep efficiency ($p < 0.01$) than the remainder of the sample (n = 72). Patients with SOREMPs-20 had higher REM percentage ($p < 0.05$) and a higher first REM period density ($p < 0.05$).

Table I. Distribution of SOREMPs by Night of Occurrence in 92 Major Depressive Inpatients

	Distribution (no. and % of nights)				
	Night 1	Night 2	Night 3	Night 4	Total
SOREMPs-10	9 (9.8%)	10 (10.9%)	11 (12.0%)	5 (5.4%)	35 (9.5%)
SOREMPs-20	16 (17.4%)	18 (19.6%)	17 (18.5%)	11 (12.0%)	62 (16.8%)
	No. and % of major depressive inpatients exhibiting SOREMPs				
	Night 1	Night 2	Night 3	Night 4	Total
SOREMPs-10	10 (10.8%)	6 (6.5%)	3 (3.3%)	1 (1.1%)	20 (21.7%)
SOREMPs-20	13 (14.1%)	8 (8.7%)	7 (7.6%)	3 (3.3%)	31 (33.7%)

Table II. Frequency of Clinical and RDC Characteristics (From SADS-L)

	n	SOREMP-10 Group (%) (*n* = 20)	RL[a] 11-20 Group (%) (*n* = 11)	Group Without SOREMP (%) (*n* = 61)	χ^2	*p*
Gender						
Male	31	45.0	36.4	29.5	1.7	ns
Female	61	55.0	63.6	70.5		
Clinical response						
Responders	65	60.0	72.7	73.8	1.4	ns
Nonresponders	27	40.0	27.3	26.2		
Primary	68	80.0	63.6	74.6	1.0	ns
Secondary	24	20.0	36.4	25.4		
Recurrent	57	70.0	72.7	57.4	1.6	ns
Psychotic	6	5.0	0.0	8.2	1.1	ns
Incapacitating	82	100.0	81.8	86.9	3.4	ns
Agitated	45	65.0	45.5	44.3	2.6	ns
Retarded	46	55.0	54.5	47.5	0.4	ns
Situational	54	50.0	72.7	59.0	1.5	ns
Simple	48	55.0	54.5	50.8	0.1	ns
Unipolar	83	85.0	100.0	91.8	2.1	ns
Bipolar I	4	0.0	0.0	6.6	2.1	ns
Bipolar II	5	15.0	0.0	3.3	4.7	0.09

[a]REM latency.

Table III. Clinical Characteristics and Severity Ratings

	SOREMP-10 Group (n = 20)		RL[a] 11-20 Group (n = 11)		Group Without SOREMP (n = 61)			
	Mean	SD	Mean	SD	Mean	SD	F	p
Clinical characteristics								
Age	42.8	13.6	40.2	12.6	33.6	10.6	3.2	0.01
Age at first onset	33.8	12.9	27.7	12.4	25.5	11.2	2.9	0.01
Illness duration (years)	9.0	7.8	14.7	12.7	8.1	8.1	1.0	ns
Number of episodes	2.3 (median = 2)	1.6	3.1 (median = 2)	2.7	2.8 (median = 2)	2.3	0.5	ns
Duration of current episode (weeks)	44.9 (median = 32)	57.8	83.8 (median = 60)	105.4	59.3 (median = 38)	62.0	0.7	ns
Severity ratings								
Baseline Hamilton[b]	37.5	10.2	33.0	10.6	34.4	10.5	1.4	ns
Final Hamilton[b]	15.0	11.3	14.9	11.2	17.6	12.1	1.0	ns
Baseline Raskin	9.0	2.4	10.2	1.9	10.0	2.0	0.8	ns
Final Raskin	7.0	2.1	7.3	1.9	7.3	2.5	0.1	ns
Baseline BPRS	13.5	5.9	11.2	3.1	11.6	4.6	0.7	ns
Final BPRS	9.5	5.7	8.4	5.2	8.4	5.2	0.4	ns
Baseline Beck	16.3	7.4	15.3	5.9	18.3	7.9	1.1	ns
Final Beck	10.4	6.7	10.6	6.7	12.2	8.1	0.4	ns

[a]REM latency.
[b]Two-rater sum.

Table IV. Selected Sleep Characteristics

Variable	SOREMP-10 Group (n = 20) Mean	SD	RL[a] 11-20 Group (n = 11) Mean	SD	Group Without SOREMP (n = 61) Mean	SD	F	p
Sleep continuity								
Sleep latency (min)	43.2	26.2	31.3	15.0	35.1	22.9	2.9	0.05
Time spent asleep (min)	317.1	57.9	335.2	44.2	339.5	40.5	3.9	0.01
Sleep efficiency (%)	78.5	13.7	81.9	12.3	85.7	8.5	4.5	0.01
Sleep architecture (%)								
Stage 3 & 4	1.1	2.4	1.5	3.5	3.0	5.0	0.9	ns
REM	26.8	6.6	28.7	5.1	24.2	6.0	3.0	0.05
REM measures								
REM latency (min)	20.3	16.2	32.7	16.1	59.4	22.0	38.6	0.001
REM activity	124.1	59.5	133.3	39.6	109.1	43.4	1.0	ns
REM density	1.40	0.56	1.43	0.55	1.27	0.42	1.0	ns
Number of REM periods	3.1	0.9	3.1	1.0	3.5	0.7	2.9	0.05
First REM period (min)	21.4	16.7	20.7	13.7	21.6	17.7	0.5	ns
REM activity, Period 1	35.4	22.0	30.2	29.2	27.0	28.6	1.6	ns
REM density, Period 1	1.54	0.54	1.32	0.57	1.22	0.51	2.8	0.05

[a]REM latency.

DISCUSSION

This study confirms the presence of the SOREMP phenomenon in a significant proportion of major depressives, as previously described in smaller samples (Schultz *et al.*, 1979; Coble *et al.*, 1981): one-fifth of the sample exhibit at least one SOREMP-10 and one-third exhibit at least one SOREMP-20 during the four recording nights. Compared to the negative results of the outpatient study of Reynolds *et al.* (1983), this study confirms that the SOREMP phenomenon is essentially found in depressive *inpatients* and therefore may represent a sign of particular severity (e.g., lack of adequate response to an outpatient treatment regimen, presence of suicidal risk, or psychotic features). However, a higher frequency of SOREMPs has been described in narcolepsy, where multiple SOREMPs constitute the pathognomonic feature, particularly during daytime nap studies (Rechtschaffen *et al.*, 1963; Montplaisir, 1976; Reynolds *et al.*, 1982). Data from Reynolds *et al.* (1982) shows that 48% of narcoleptics present a SOREMP-10 during the second recording night compared to 10.9% in the present sample of major depressives. Moreover, in this study, only 10.9% of patients exhibit multiple SOREMPs-10 (i.e., 2 SOREMP-10) and 18 (19.6%), multiple SOREMPs-20 (i.e., 2 SOREMPs-20).

The current data do not show the clear-cut bimodal distribution of REM latency in depressives previously described by Schulz *et al.* (1979) and Coble *et al.* (1981). This apparent contradiction may result from the low representation of psychotic depressives in this study. Although the proportion of delusional depressives in the sample of Schulz *et al.* was not reported, 5 of the 22 patients (22.7%) studied by Coble *et al.* exhibited psychotic features (compared to 6.5% in this sample). Delusional depressives might represent a subgroup characterized specifically by the highest rate of SOREMPs (Coble *et al.*, 1981) and thus might be responsible for the apparent bimodal distribution of REM latency in these studies. The present study also suggests that in major depressives (delusionals excluded), REM latency is a continuous rather than discontinuous variable, different from the evident bimodal distribution reported in narcolepsy (Montplaisir, 1976) or in babies (Salzarulo and Fagioli, 1980).

With regard to clinical characteristics of depressives exhibiting SOREMPs, the older age of SOREMP-positive depressives is consistent with previous reports of an age-dependent decrease in the REM latencies of major depressives (Ulrich *et al.*, 1980; Gillin *et al.*, 1981; Kupfer *et al.*, 1982). Moreover, although the small representation of bipolar depressives ($n = 9$) in this sample does not permit a definite conclusion, the data suggest that there may be some association between SOREMP positivity and a bipolar II history. These data may be consistent with the hypothesis of cholinergic hypersensitivity in depression (as evidenced by a more rapid cholinergic REM induction response to arecoline) which was initially based on data from a sample composed mostly of bipolar depressives (Sitaram *et al.*, 1980). Finally, SOREMP-positive depressives also

present more sleep continuity disturbance than SOREMP-negative depressives. This finding is generally more prominent in psychotic than in nonpsychotic depressives and in older than younger depressives (Kupfer *et al.*, 1982; 1983b). The higher REM density during the first part of the night in SOREMP-positive depressives may also be related in part to the older age of these depressives, suggesting, as Vogel (1975) has speculated, that the capacity to sustain REM sleep inhibition diminishes with age.

The lack of greater symptom severity among SOREMP-positive depressives is somewhat surprising in view of previous reports suggesting an inverse relationship of REM latency to severity of depression (Kupfer and Foster, 1972; Spiker *et al.*, 1978), as well as limited data from Schulz and Tetzlaff (1982) showing that nine patients exhibiting SOREMPs described themselves as significantly more depressed than seven patients without SOREMPs. However, this finding has not been replicated in depressive outpatients (Akiskal *et al.*, 1982). In fact, these discrepancies may result from the absence of psychotic depressives in outpatient studies as well as the low representation of psychotic depressives in this sample. Psychotic depressives, who obtained higher scores in standard rating scales of depression (e.g., the Hamilton Depression Scale), are characterized by very short REM latencies (Snyder, 1972; Kupfer *et al.*, 1982a). Thus, the inverse relationship noted between REM latency and severity of depression may result from the inclusion of two qualitatively distinct subtypes of patients: psychotics and nonpsychotics.

In the same way the absence of an obvious relationship between SOREMP positivity and clinical response to standard tricyclic antidepressant therapy may result from the low number of delusional depressives in the sample, who in general respond poorly to tricyclics and often need more aggressive types of treatment (Nelson and Bowers, 1978; Glassman and Roose, 1981). The hypothesis that psychotic depressives present a high frequency of SOREMPs, responsible for the suggested association of SOREMP positivity with higher symptom severity and poor clinical response (Coble *et al.*, 1981), needs to be tested in a separate study, which would also control for age-related variability in SOREMP positivity and clinical response.

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