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SLEEP ELECTROENCEPHALOGRAPHY AND THE CLINICAL RESPONSE TO AMITRIPTYLINE IN PATIENTS WITH FIBROMYALGIA

SIMON CARETTE, GERALD OAKSON, CHANTAL GUIMONT, and MIRCEA STERIADE

Objective. **To determine the prevalence and clinical correlations of an anomaly consisting of electroencephalographic (EEG) waves within the alpha frequency band during non–rapid eye movement (NREM) sleep in patients with fibromyalgia, and to evaluate the alpha NREM sleep anomaly as a predictor of response to amitriptyline.**

Methods. **Twenty-two patients with fibromyalgia were studied in a 2-month, double-blind, crossover trial of amitriptyline (25 mg/day) versus placebo. Nocturnal EEGs were conducted on 2 consecutive nights at baseline and at the end of each 2-month treatment period.**

Results. **Six patients (27%) had a clinical response to amitriptyline, while none responded to placebo ($P = 0.02$). Treatment with amitriptyline or placebo did not result in any changes in the alpha ratings during NREM sleep. Only 8 patients (36%) exhibited the alpha NREM sleep anomaly at baseline. Those patients reported more sleep difficulty, but otherwise were clinically indistinguishable from those without this EEG sleep anomaly. Lower baseline alpha NREM sleep ratings were seen in responders to amitriptyline than in nonresponders, but these differences did not reach statistical significance.**

Conclusion. **The alpha NREM sleep anomaly is present in only a small proportion of patients with fibromyalgia. It does not correlate with disease severity nor is it affected by treatment with amitriptyline. A larger sample size will be needed to adequately assess the value of this sleep anomaly in predicting the response to amitriptyline.**

Sleep disturbance has been suggested to play a central role in the pathophysiology of fibromyalgia. The vast majority of patients with this condition feel unrested upon awakening in the morning and report having chronic fatigue (1,2). Distinct sleep anomalies on electroencephalography (EEG) in patients with fibromyalgia have been described by Moldofsky and associates (3,4) and have since been confirmed by numerous other investigators (5–7). These anomalies consist of intrusion of alpha waves during stages 2, 3, and 4 of non–rapid eye movement (NREM) sleep, the so-called alpha NREM sleep anomaly.

Amitriptyline, a tricyclic antidepressant agent with well-documented effects on both REM and NREM sleep, has been shown to improve sleep and decrease pain and stiffness in 20–30% of patients with fibromyalgia (8–12). Whether amitriptyline has an effect on the occurrence of the alpha NREM sleep anomaly is presently unknown.

This study was designed to answer the following questions: 1) What is the prevalence of the alpha NREM sleep anomaly in patients with fibromyalgia? 2) Does the alpha NREM sleep anomaly correlate with symptom severity? 3) Is the alpha NREM sleep anomaly stable over time? 4) Can the alpha NREM sleep anomaly predict the response to amitriptyline in patients with fibromyalgia? 5) Does the response to amitriptyline correlate with changes in the alpha NREM ratings?

PATIENTS AND METHODS

Patients were recruited from the outpatient rheumatology clinic of Laval University Hospital. The sleep studies were conducted at the sleep laboratory of the Laval University Chest Institute. The protocol was approved by the 2

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Simon Carette, MD, Gerald Oakson, BSc, Chantal Guimont, Msc, Mircea Steriade, MD, DSc: Laval University, Sainte-Foy, Quebec, Canada. Dr. Carette is a Senior Scholar of the Fonds de la Recherche en Santé du Québec.

Address reprint requests to Simon Carette, MD, 2705 Boulevard Laurier, Sainte-Foy, Quebec, Canada G1V 4G2.
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institutional ethics committees, and all patients gave written informed consent.

Patient selection criteria. Patients were eligible for the study if they were 18 years of age or older and met the American College of Rheumatology 1990 criteria for the classification of fibromyalgia (13). In addition, patients had to have a score of >4 on at least 1 of 2 self-administered 10-cm visual analog scales (1 evaluating pain and 1 evaluating global assessment of fibromyalgia symptoms). Normal results on measurements of the erythrocyte sedimentation rate, creatine phosphokinase level, and thyroid-stimulating hormone level were required. Four of the 22 patients studied had previously participated in a multicenter trial comparing amitriptyline, cyclobenzaprine, and placebo (12).

Patients were excluded from the study if they showed evidence of neurologic, muscular, infectious, endocrine, osseous, or other inflammatory rheumatic diseases. Patients with a history of glaucoma, urinary retention, myocardial infarction, arrhythmia, or congestive heart failure were also excluded, as were patients with known sleep apnea syndrome.

Nonsteroidal antiinflammatory drugs and hypnotic drugs were discontinued a minimum of 2 weeks before entry into the study. Antidepressant agents were discontinued a minimum of 1 month before study entry. Only acetaminophen was permitted during the study, and a letter was sent to the referring physician explaining the importance of limiting concurrent interventions.

The control group consisted of 9 healthy women, matched for age, who were recruited from hospital staff. None reported any symptoms of pain or sleep disorders.

Study design. We used a double-blind, crossover trial design of 8 weeks' duration. Each patient was randomly assigned to receive either amitriptyline 25 mg/day, 1 hour before bedtime or an identical-appearing inert placebo. The order of treatment (amitriptyline first or placebo first) was generated using a table of random numbers. No washout period was instituted between the two 8-week treatment periods since it was not expected that amitriptyline would affect patients' symptoms and sleep parameters evaluated 2 months after cessation of this treatment. In the event of adverse reactions or intolerability, the daily dosage of amitriptyline was reduced from 25 mg to 10 mg.

Assessment of sleep parameters and EEG activity. Each patient was asked to sleep 6 nights at the sleep laboratory (2 nights at baseline, and 2 nights after each 8-week treatment period). The controls slept 1 night at the laboratory. They were studied by means of continuous nightly recording of their EEG (C3/A2, C4/A1), electrooculogram (right and left outer canthi), and submental electromyogram. Paper speed was 15 mm/second, and all records were scored blindly in 40-second epochs according to standard criteria (14). The following variables were calculated: total sleep time, sleep latency/sleep onset, delta latency, REM latency, and percentage of time spent in each sleep stage. Ratings of alpha-region (7.5–11 Hz) EEG for sleep stages 3 and 4 over the entire night were scored on a scale of 1 (up to 20% per epoch) to 5 (>80% per epoch) by one trained observer. Randomly selected epochs from sleep stage 2, covering an average of 30 minutes per patient, were also scored.

Followup and assessment of outcome. Patients were evaluated at baseline and at the end of weeks 8 and 16. The same physician (SC) examined each patient throughout the study.

Patients' assessments included four 10-cm visual analog scales evaluating pain (0 = none; 10 = severe), fatigue (0 = none; 10 = extreme fatigue), sleep (0 = no difficulty; 10 = extreme difficulty), and global assessment of fibromyalgia (0 = not troublesome at all; 10 = extremely troublesome). The physician's assessments included a measurement of fibromyalgia point tenderness on 10 (5 paired) points, with the aid of a 9-kg dolorimeter (Chatillon, New York, NY) as previously described (8). The individual scores were summed to give the total myalgic score. The physician also made a global assessment of fibromyalgia using a 10-cm visual analog scale (0 = doing extremely well; 10 = doing extremely poorly).

Clinical analysis. Based on previous work by Simms et al (15), a patient was considered to have significant improvement if 4 of the following 6 criteria were met: 50% improvement in pain, sleep, fatigue, patient global assessment, or physician global assessment, and increase of 1 kg in mean total myalgic score. Only the sleep data obtained from the second night of paired nights were used for the analysis, the first night being considered a habituation night.

Statistical analysis. Data were analyzed using the SAS software system (6.08 version). Baseline continuous variables were compared between patients and controls using Student's 2-tailed *t*-test, while categorical data were compared by chi-square analysis. The major end point for assessing efficacy was compared between the 2 treatment groups using Fisher's chi-square 2-tailed exact test. Analyses of variance on changes from baseline to the end of each treatment and between treatment groups were performed for visual analog scores, tender point scores, and sleep data. Variables measured at baseline were compared between responders and nonresponders using Student's 2-tailed *t*-test. Logistic regression was used in an attempt to find predictors of response to amitriptyline.

Computer analysis of EEG activity. As a parallel project, frequency characteristics of EEG activity were computed using the Fast Fourier Transform (FFT) method (16). FFTs of the control subjects, the patients at baseline, and the patients after amitriptyline administration were analyzed from tape recordings. Periods from EEGs previously scored visually as sleep stage 3 or 4 were selected for the computer database and consisted of contiguous segments of 32 seconds, selected around the center of each epoch. To conserve computer space, all available segments were retained for the shorter epochs (lasting up to 320 seconds), but for longer epochs, data were chosen up to a maximum of 640 contiguous seconds around the center of the epoch. The selected data were filtered from 0.5 to 20 Hz, digitized at 64 samples/second, and stored in the computer.

To ensure equal weighting of subjects, the same duration of EEG should be analyzed for each subject in a group. Since the quantity of data available for each subject varied greatly, a tradeoff between the number of subjects analyzed and the duration per subject was necessary. A longer analysis duration per subject reduces the number of eligible subjects. For those subjects having more data than

Table 1. Characteristics of the 22 fibromyalgia patients at baseline*

Age, years	43.8 ± 8.0
Duration of fibromyalgia, months	82.7 ± 75.4
Sex (% female)	95.5
Education level, years	13.1 ± 4.2
No. of children	2.3 ± 1.7
No. of tender points	16.0 ± 2.17
Symptoms (% reporting)	
Headaches	77.3
Bowel syndrome	54.5
Paresthesia	68.2
Subjective swelling	77.3
Employment status (%)	
At work	27.3
Not at work	72.7
Due to fibromyalgia	22.7
Other reason	50.0

* Unless otherwise indicated, values are the mean ± SD.

the chosen duration, the segments to be analyzed were randomly selected from the available data. This selection resulted in data from 7 controls (29 segments/subject, 108 minutes total), and from 15 patients at baseline (18 segments/subject, 144 minutes) and after amitriptyline treatment (16 segments/subject, 128 minutes). The same subjects were analyzed in the patient baseline and amitriptyline groups.

Individual FFTs, covering the spectral range from 0.5 to 20 Hz with a bin width of 0.5 Hz, were computed on each 32-second segment of selected EEG data. To maximize sample size, statistical comparisons of spectra between groups were performed using the individual FFTs from each subject, rather than their average. The comparisons were done on a bin-by-bin basis, using Student's 2-tailed *t*-test, by comparing the values in a given frequency bin in all FFTs in one group with the corresponding values in the same bin in all FFTs in the second group.

RESULTS

Demographic and clinical features. Twenty-two fibromyalgia patients were studied. Their baseline demographic and clinical characteristics are shown in Table 1. All members of the control group were female, and their mean age (±SD) was 36.7 ± 5.0 years. One control subject had 2 tender points, and the remaining 8 had none.

Two of the 22 patients failed to complete the study according to the protocol. Each of these 2 patients was evaluated after completion of the first 2 months of treatment (both were receiving amitriptyline), but refused, for personal reasons, to return for the second arm of the study. Based on pill counts, there were no protocol violations. Only 1 patient decreased the study medication dosage (on the amitriptyline arm).

Six patients (27.3%) showed significant improvement with amitriptyline treatment, versus none with placebo treatment ($P = 0.02$). Table 2 shows the changes in the visual analog scale scores with each treatment. Patients receiving amitriptyline showed significant improvement over baseline scores for each of the variables with the exception of total myalgia score. No improvement was observed with placebo. The differences between the 2 treatments were statistically significant for each of the variables except total myalgia scores.

Table 3 shows the sleep characteristics of the patients at baseline and after each treatment, and of the controls. There was a statistically significant difference in the alpha ratings between patients and controls at baseline, with the patients showing higher rates of alpha than the controls in stages 3 and 4 NREM sleep. None of the alpha ratings were affected by treatment with either amitriptyline or placebo. Compared with baseline, the percentage of stage 2 sleep was increased in patients treated with amitriptyline, and sleep latency decreased in patients receiving placebo, but otherwise, no changes in any of the sleep parameters were seen.

The patients were divided into 2 groups according to their alpha EEG ratings at baseline: 1 group consisted of patients with alpha ratings in the same range as the controls (n = 14), and the other comprised patients with alpha ratings at least 2 standard deviations above that of the controls (n = 8). The differ-

Table 2. Clinical characteristics of the patients at baseline and after amitriptyline or placebo treatment*

	Baseline (n = 22)	Amitriptyline (n = 22)	Placebo (n = 20)
% responders	–	27.3	0
Pain	7.12 ± 1.90	5.07 ± 3.22†	7.13 ± 2.41‡
Fatigue	7.84 ± 1.80	5.62 ± 3.07†	7.64 ± 1.80‡
Sleep	7.49 ± 2.77	3.93 ± 3.14†	6.51 ± 2.69‡
Patient global evaluation	7.27 ± 1.69	5.47 ± 3.03†	7.11 ± 2.14‡
Physician global evaluation	6.40 ± 1.65	4.81 ± 2.81†	6.36 ± 1.59‡
Total myalgic score	3.18 ± 0.74	3.45 ± 1.16	3.22 ± 0.86

* Values for pain, fatigue, sleep, patient global evaluation, and physician global evaluation are from 10-cm visual analog scales. Total myalgic score is the sum of point tenderness at 10 points. Except for the % responders, values are the mean ± SD.
† $P < 0.05$ versus baseline value, by Tukey's studentized range test.
‡ $P < 0.05$ versus amitriptyline treatment, by Tukey's studentized range test.

Table 3. Sleep characteristics of the control subjects and of the patients at baseline and after amitriptyline or placebo treatment*

	Controls (n = 9)	Baseline (n = 22)	Amitriptyline (n = 22)	Placebo (n = 20)
Total sleep time, hours	6.58 ± 0.9	6.34 ± 1.1	6.76 ± 1.2	6.48 ± 1.1
% stage 1	6.70 ± 3.7	7.45 ± 5.0	8.14 ± 4.2	5.55 ± 2.8†
% stage 2	49.74 ± 6.4	46.57 ± 7.5	51.73 ± 9.7‡	47.51 ± 7.0
% stage 3	7.71 ± 2.6	7.24 ± 2.7	6.66 ± 1.9	7.69 ± 2.4
% stage 4	17.22 ± 7.8	16.35 ± 7.6	13.75 ± 7.0	16.44 ± 6.1
% REM	18.72 ± 4.0	22.46 ± 7.3	19.82 ± 7.0	22.83 ± 5.7
Latency sleep, minutes	11.78 ± 9.8§	23.36 ± 15.6	20.60 ± 13.1	13.32 ± 11.9‡
Latency stage 3, minutes	34.22 ± 32.8	34.23 ± 35.5	28.60 ± 23.6	19.32 ± 8.8
Latency stage 4, minutes	47.22 ± 35.9	35.43 ± 26.6	36.84 ± 24.0	35.63 ± 24.8
Latency REM, minutes	149.8 ± 87.1	95.52 ± 44.1	98.37 ± 52.3	89.84 ± 45.3
Stage 2 alpha rating	1.79 ± 0.7	2.32 ± 0.7	2.47 ± 0.8	2.20 ± 1.2
Stage 3 alpha rating	1.72 ± 0.3§	2.22 ± 0.8	2.19 ± 0.9	2.34 ± 0.7
Stage 4 alpha rating	1.29 ± 0.3§	1.67 ± 0.7	1.72 ± 0.7	1.90 ± 0.8
Stages 3 or 4 alpha rating	1.46 ± 0.3§	1.96 ± 0.8	2.01 ± 0.8	2.04 ± 0.8

* Values are the mean ± SD. REM = rapid eye movement.
† $P \leq 0.05$ versus amitriptyline treatment, by Tukey's studentized range test.
‡ $P \leq 0.05$ versus baseline value, by Tukey's studentized range test.
§ $P \leq 0.05$ versus baseline value, by Student's t-test.

ences between the 2 groups, with 95% confidence intervals, are shown in Table 4. Patients with higher alpha ratings reported worse scores for all parameters with the exception of pain. The differences between the groups were higher for sleep analog scores, but none reached statistical significance.

The mean alpha NREM EEG ratings at baseline were compared in amitriptyline responders and nonresponders (Table 5). The ratings were lower in responders, but the differences were not significant. Treatment with amitriptyline resulted in a decrease of the alpha ratings in only 2 of the responders. In the other 4 responders, the alpha ratings remained unchanged (n = 2) or increased (n = 2).

Using logistic regression, the number of tender points (<18 versus 18 points) was the only variable among the demographic, clinical, and EEG parameters measured at baseline that was associated with response to amitriptyline.

Findings of computer analysis. Figure 1 shows stage 3 frequency spectra from the control group versus the patient group at baseline, and from the patient group at baseline versus after amitriptyline treatment, along with their spectral differences. The differences between the patient baseline values and the control values indicated a significant increase in alpha activity (the 9–12.5-Hz region) in the patient baseline group compared with controls, with a lesser increase in the 5–6-Hz and 16–20-Hz regions. The differences in the patient group after amitriptyline treatment versus at baseline showed no significant change in alpha components with amitriptyline, but a pronounced decrease in delta activity (1.5–4 Hz) was evident. Stage 4 results were similar.

Table 4. Clinical characteristics of the patients with normal alpha ratings and the patients with abnormal alpha ratings*

	Normal alpha (n = 14)	Abnormal alpha (n = 8)	Difference (95% CI)
% responders to amitriptyline	28.6	25.0	–
Pain	7.16 ± 1.49	7.06 ± 2.58	0.10 (−1.70, 1.90)
Fatigue	7.73 ± 1.85	8.04 ± 1.80	−0.31 (−2.00, 1.38)
Sleep	6.76 ± 3.20	8.76 ± 1.00	−2.00 (−4.45, 0.45)
Patient global evaluation	7.09 ± 1.68	7.58 ± 1.78	−0.49 (−2.08, 1.10)
Physician global evaluation	6.26 ± 1.41	6.67 ± 2.16	−0.41 (−1.99, 1.17)
Total myalgic score	3.21 ± 0.74	3.12 ± 0.79	0.09 (−0.61, 0.79)

* Alpha ratings >2 SD above the mean in controls were considered abnormal. Except for the % responders, values are the mean ± SD. 95% CI = 95% confidence interval. See Table 2 for details.

Table 5. EEG alpha ratings at baseline in amitriptyline responders and nonresponders*

	Responders (n = 6)	Nonresponders (n = 16)	Difference (95% CI)
Stage 2 alpha rating	2.05 ± 0.65	2.42 ± 0.72	−0.37 (−1.07, 0.33)
Stage 3 alpha rating	1.82 ± 0.46	2.36 ± 0.81	−0.54 (−1.28, 0.20)
Stage 4 alpha rating	1.49 ± 0.49	1.73 ± 0.76	−0.24 (−0.94, −0.46)
Stages 3 or 4 alpha rating	1.61 ± 0.46	2.09 ± 0.81	−0.48 (−1.22, 0.26)

* Values are the mean ± SD. EEG = electroencephalography; 95% CI = 95% confidence interval.

DISCUSSION

The present study confirms that, as a group, patients with fibromyalgia have increased ratings of the alpha EEG NREM sleep anomaly compared with age- and sex-matched controls. The significance of this sleep anomaly remains unknown. It is not specific for fibromyalgia: it has been described in healthy individuals (17) as well as in patients with other rheumatic conditions such as osteoarthritis (18) and rheumatoid arthritis (19,20). It has been suggested that the alpha EEG NREM sleep anomaly could be induced by pain and/or psychologically distressing situations (21). Interestingly, subjects with chronic insomnia do not appear to have this sleep anomaly (22).

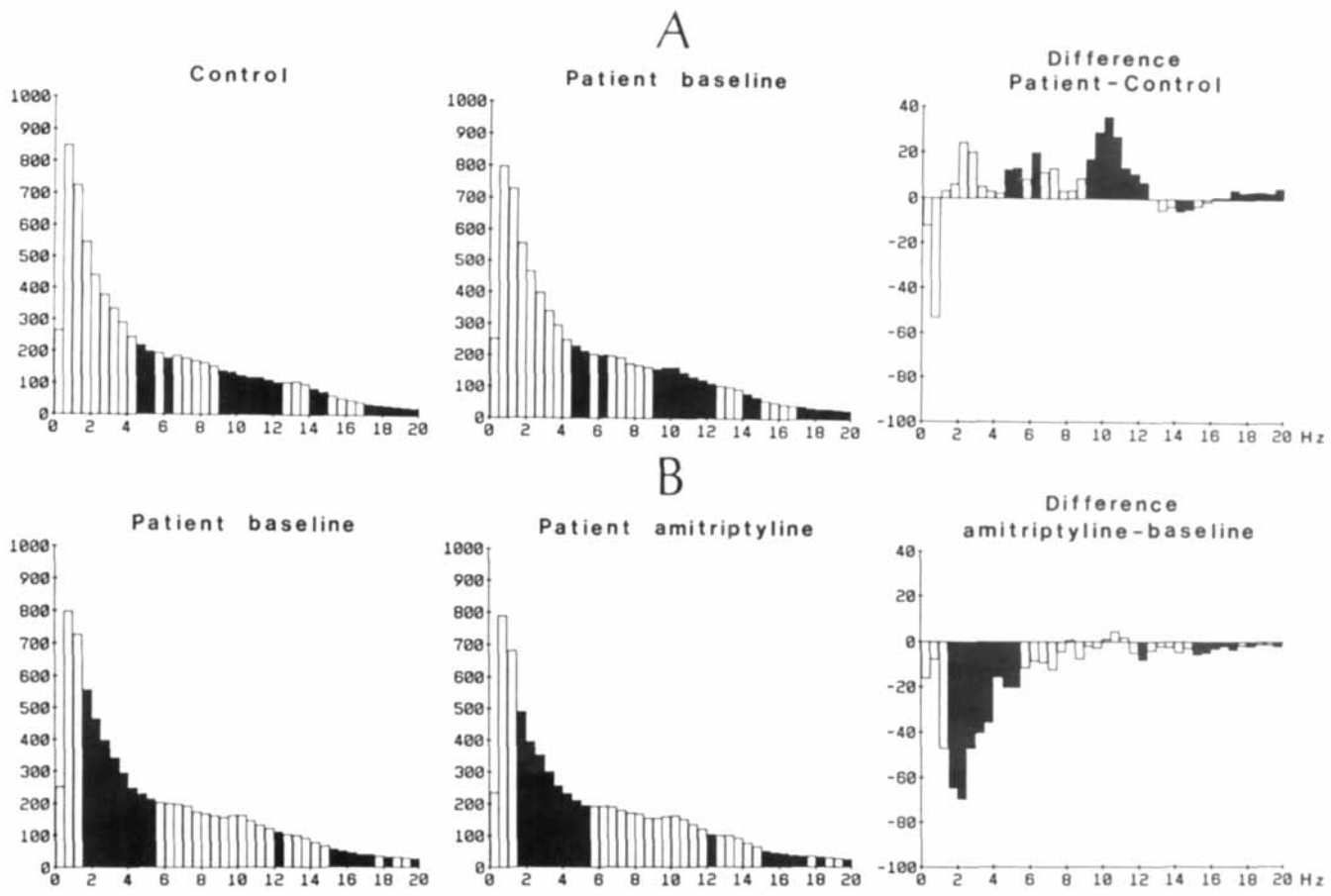

Figure 1. Averaged frequency spectra of electroencephalography waves from channels C3–A2 and their differences, for 7 controls and 15 patients during stage 3 sleep. **A**, Fast Fourier Transform values (FFTs) in the control group and in the patient group at baseline, and their difference. **B**, FFTs in the patient group at baseline and in the same patients after amitriptyline treatment, and their difference. Abscissas are in bins of 0.5 Hz; ordinates are in arbitrary but comparable units. Black bins, which indicate significant spectral differences between groups, were computed using Student's 2-tailed *t*-test (see Patients and Methods). Stage 4 sleep showed similar results.

An interesting and important finding of this study is the demonstration that a substantial subgroup of patients with fibromyalgia (14 of 22; 64%) could not be differentiated from healthy individuals on the basis of sleep EEG findings since they did not demonstrate the alpha EEG NREM sleep anomaly. The patients with the alpha EEG NREM sleep anomaly reported more sleep difficulty than did those without this anomaly (mean score of 8.76 versus 6.76; $P = 0.06$), but they could not be differentiated on the basis of their pain, fatigue, myalgic scores, or global assessment scores. Although these findings support the possibility that the alpha NREM EEG sleep anomaly could be related to the morning symptoms of nonrestorative sleep frequently reported by patients with fibromyalgia, it does not prove a causal relationship. The fact that the alpha EEG sleep ratings decreased in only 2 of the patients whose fibromyalgia improved with amitriptyline tends to minimize the role of this sleep anomaly in the pathophysiology of fibromyalgia. The alpha EEG NREM sleep anomaly appears to be stable over time. After 2 months of placebo treatment, patients showed similar alpha ratings as compared with baseline, both as a group and individually.

The computed results suggest similar conclusions to those obtained from visual scoring, i.e., there is significantly higher alpha activity in the patient group at baseline compared with controls, and amitriptyline treatment does not result in a decrease in alpha activity over baseline.

The findings of this trial with respect to the efficacy of amitriptyline are comparable with those of a large Canadian multicenter trial that has recently been reported (12). Using the same criteria for improvement as those used in the current study, 22% of the patients receiving amitriptyline and 10% of the patients receiving placebo in that trial were significantly improved after 2 months, as compared with 27% and 0%, respectively, in this trial (12). In both trials, myalgia scores did not improve over baseline scores.

Attempts to identify predictors of response to amitriptyline in patients with fibromyalgia have thus far been unsuccessful. In the Canadian multicenter trial, none of many demographic, clinical, functional, and psychological features measured at baseline was able to predict treatment outcome (12). The results of the present study suggest that the alpha EEG NREM sleep anomaly is not helpful in predicting the clinical response to amitriptyline. Virtually the same proportion of patients with and without this sleep anomaly responded to the drug (25% and 29%, respectively). On the other hand, the mean alpha NREM EEG ratings were lower at baseline in responders than nonresponders. While the difference was not statistically significant, this clearly could be due to a Type II error. A sample size of 60 patients, rather than 22, would have been needed to detect a significant difference between these means with a power of 80%.

We conclude that the alpha EEG NREM sleep anomaly is found in only a small proportion of patients with fibromyalgia. When present, it correlates with more self-reported sleep disturbance, but not with other symptoms or signs of fibromyalgia. This sleep anomaly is not affected by treatment with amitriptyline. A large sample size would be needed to adequately assess the value of the alpha EEG NREM sleep anomaly in predicting the response to amitriptyline. The precise role of sleep disturbances in the pathophysiology of fibromyalgia has yet to be elucidated.

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