Polysomnography With Quantitative EEG in Patients With and Without Fibromyalgia

Victor W. Rosenfeld, Dana N. Rutledge,† and John M. Stern‡*

Purpose: Characterize the polysomnographic (PSG) and quantitative EEG (qEEG) features of fibromyalgia and determine whether fibromyalgia patients differ in these measures when compared with a control sleep disorder population.

Methods: All undergoing all-night PSG for evaluation of a sleep disorder were evaluated for fibromyalgia. The PSGs were interpreted for routine sleep measures, and qEEG was performed to measure the delta and alpha frequency power during non-rapid eye movement sleep. Measures and qEEG were analyzed according to fibromyalgia diagnosis.

Setting: Community-based sleep medicine center.

Patients: All patients undergoing PSG over a 2-year period.

Interventions: None.

Results: Of the 385 patients in the study population, 133 had fibromyalgia according to American College of Rheumatology criteria. The population's average Epworth Sleepiness Score was 10.5, the average sleep efficiency was 78%, and the Periodic Limb Movement disorder prevalence was 15%. None of these sleep measures differed significantly between the fibromyalgia and non-fibromyalgia groups. Obstructive sleep apnea was present in 45% of the fibromyalgia group. Significant differences were present in the qEEG ratio of delta to alpha frequency power, which was 95% specific for fibromyalgia when ≤1. A qEEG ratio ≤10.5 was 85% sensitive for fibromyalgia, and a qEEG ratio >10.5 had an 89% negative predictive value for fibromyalgia. Among patients with fibromyalgia who were not taking a benzodiazepine or benzodiazepine agonist, a qEEG ratio ≤10.5 was 84% specific and had a 78% positive predictive value.

Conclusions: Sleep disorders identified by routine PSG, including obstructive sleep apnea, are common in fibromyalgia, but periodic leg movement disorder and poor sleep efficiency are not. A qEEG low delta/alpha ratio during non-rapid eye movement sleep can differentiate patients with fibromyalgia from others who are referred for PSG. Consideration of benzodiazepine and benzodiazepine agonist use is important when interpreting the delta/alpha ratio.

Key Words: Polysomnography, Quantitative EEG, Sleep, Fibromyalgia.

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Fibromyalgia is the most common widespread pain syndrome in the world, affecting 2% to 6% of the population (Farooqi and Gibson, 1998; International Classification, 2005; Lindell et al., 2000; Senna et al., 2004; White and Thompson, 2003; Wolfe et al., 1995). Between 30% and 50% of people diagnosed with fibromyalgia are disabled, and the total cost to the US economy has been assessed to be approximately $10 billion annually (Robinson et al., 2003). The diagnosis of fibromyalgia is based on the 1990 American College of Rheumatology (ACR) criteria, which consists of subjective pain complaints and a Manual Tender Point Examination. However, numerous other symptoms and comorbid conditions are widely acknowledged to be present (Hauser et al., 2008). A recent survey of 2,596 patients with fibromyalgia showed that the most prevalent complaints, in order, were morning stiffness, fatigue, nonrestorative sleep, followed by pain, and forgetfulness (Bennett et al., 2007). Overall, the association between fibromyalgia and sleep abnormality has been recognized in medical publications since at least 1869 (Hartshorne, 1869).

Fibromyalgia is considered to be a medical disorder by the American Medical Association and the World Health Organization; however, controversy lingers about its basis. The lack of a biomarker or routine diagnostic laboratory test impedes general acceptance and complicates diagnosis, assessment of severity, and measurement of treatment response. Currently, the only laboratory abnormality for fibromyalgia is polysomnography (PSG), which was first reported in 1975 with the recognition of an association between fibromyalgia and alpha frequency EEG activity intruding into slow wave non-rapid eye movement (REM) sleep (Roizenblatt et al., 2001). Subsequently, it was recognized that symptoms of fibromyalgia, including diffuse musculoskeletal pain and fatigability, occur when healthy volunteers are deprived of slow-wave sleep (Moldofsky and Scarisbrick, 1976; Moldofsky et al., 1975). Relationship of fibromyalgia to dysfunctional slow-wave sleep was further supported through the observation that significantly increasing slow-wave sleep with sodium oxybate, a novel endogenous neuropeptide and potent GABA-B agonist, reduced daytime pain and fatigue and improved quality of life measures in patients with fibromyalgia (Russell et al., 2009a; Scharf et al., 2003). There is currently no consensus for quantifying alpha intrusions during sleep or for the limits of normal alpha intrusion, nor is there any large community-based study identifying the prevalence of sleep disorders in fibromyalgia.

We used nocturnal PSG to investigate quantitative EEG (qEEG) and commonly obtained PSG measures as laboratory markers for fibromyalgia in a large sample of patients referred for routine PSG at a community-based sleep medicine center. Nocturnal PSG is widely available and often has the capability of including qEEG. The software necessary for qEEG is commonly found as a standard tool in newer PSG analysis software packages. A reliable and available marker for fibromyalgia could provide an objective means to both verify diagnosis and track severity for the large population of patients who are affected by fibromyalgia.

METHODS

The study approval was granted by the Institutional Review Board of Cottage Hospital, Santa Barbara, CA and registered on

From the *SouthCoast Medical Group, Savannah, Georgia, U.S.A.; †School of Nursing, California State University, Fullerton, California, U.S.A.; and ‡University of California, Los Angeles, California, U.S.A.

Address correspondence and reprint requests to John M. Stern, MD, UCLA Department of Neurology, 710 Westwood Plaza, Suite 1250, Los Angeles, CA 90095, U.S.A.; e-mail: jstern@ucla.edu.

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clinicaltrials.gov (NCT01674179). The cohort was derived from a consecutive patient population that was referred to a single community-based sleep medicine center for PSG over the 2-year period from January 1, 2008 to December 31, 2009. Inclusion criteria were age between 15 and 75 years and completion of a routine PSG. There was no inclusion or exclusion criterion for body mass index (BMI), medications, fatigue, depression, or medical history. The cohort totaled 527 consecutive patients with a variety of PSG indications, most commonly being daytime sleepiness, snoring, witnessed apnea, sleep-disturbing periodic leg movements, and a diagnosis of fibromyalgia. Patients on sodium oxybate were excluded from the study as sodium oxybate has been previously reported to reduce the Delta/Alpha (D/A) Event Ratio, which was a study measure (Rosenfeld et al., 2010; Scharf et al., 2003).

Clinical Data

The data set included age, gender, medications, BMI, Epworth Sleepiness Scale score, and whether there was a diagnosis of fibromyalgia or chronic pain. Medications were grouped as (1) benzodiazepines or benzodiazepine agonists and (2) antidepressants, including tricyclic antidepressants, serotonin-specific reuptake inhibitors, and serotonin–norepinephrine reuptake inhibitors. Patients with either a diagnosis of fibromyalgia or who reported chronic, widespread pain were screened for fibromyalgia and underwent a Manual Tender Point Examination including 18 anatomical specific tender points as well as 3 control points (Wolfe et al., 1990). All assessments were performed by a single physician (V.R.) who is a rated Manual Tender Point Examiner for clinical trials. Patients were also considered to have fibromyalgia if they had fewer than 11 tender points but gave a history of chronic pain and were on treatment with pain modifying medication or Food and Drug Administration-approved medication for the treatment of fibromyalgia. Patients without complaints of chronic pain or fibromyalgia were not referred for Manual Tender Point testing. Nineteen patients reported chronic pain and had at least 11 of 18 tender points but had 3 of 3 positive control points and were not included as fibromyalgia subjects in the analyses and were excluded from the study. Persons without fibromyalgia who had severe obstructive sleep apnea (OSA) defined as an Apnea/Hypopnea Index greater than 30 ($n = 123$) were also excluded from the study. The final study sample was 385 patients.

Sleep Testing

An all-night comprehensive PSG was performed using a Healthdyne Alice 5 computerized polygraph (Respironics, Pittsburgh, PA) recording from standard PSG locations, including EEG electrodes at C3, Cz, Oz, and Fz, and additional electrodes/sensors for left and right electrooculogram, submental and tibialis anterior electromyogram, electrocardiogram, nasal/oral airflow, oxygen saturation (pulse oximetry), chest and abdominal effort belts, sonogram (snoring), and body position monitor. EEG was recorded with a 500-Hz sampling rate and a frequency response of 0.3 to 106 Hz. Patients with excessive daytime sleepiness and an Epworth Sleepiness Scale score greater than 10 that was unexplained by the preceding nights' sleep underwent a Multiple Sleep Latency Test according to criteria set forth by the American Academy of Sleep Medicine (Littner et al., 2005).

All studies were attended by a registered PSG technologist and scored by one investigator (M.H.) after the raw data were manually reviewed and interpreted by a single physician who is a Diplomate with Subspecialty Certification in Sleep Medicine (V.R.). Sleep stages were scored manually in 30-second epochs according to standard criteria (Rechtshaffen and Kales, 1968). Sleep Study Data Points included Total Sleep Time, Sleep Efficiency, Wake After Sleep Onset, Apnea/Hypopnea Index, Respiratory Distress Index, Periodic Limb Movement (PLM) Index with and without Arousal, and qEEG: D/A Event Ratio. Quantitative EEG methods conformed to the American Academy of Neurology's report on the use of qEEG for clinical and scientific purposes (Nuwer, 1997).

Delta/Alpha Event Ratio

Quantitative EEG analysis used a Fourier decomposition of the whole signal into frequency spectra for the alpha (8–13 Hz) and delta frequency (<4 Hz) ranges across all non-REM sleep stages of a patients sleep study using data from all of the PSG's EEG electrodes (C3, Cz, Oz, and Fz). Low frequency filter was set at 1 Hz and high frequency filter was set at 70 Hz. A delta event (D) was defined by the Respironics Alice 5 qEEG module as five cycles of continuous delta frequency range activity during non-REM sleep, and an alpha event (A) was defined as five cycles of continuous alpha frequency range activity during non-REM sleep. The non-REM sleep periods were identified through the sleep scoring, so the analysis did not include events during wakefulness or REM sleep. The total delta events (D) and alpha events (A) were determined for non-REM sleep over each patient's entire sleep study. The D/A ratio was electronically calculated by dividing total delta events (D) by total alpha events (A) for each patient's entire non-REM sleep time to produce a single number.

Statistical Analysis

Characteristics of the patient group were summarized by counts and percentages for categorical variables and by mean values and SDs for continuous variables. Differences between those with and without fibromyalgia and for demographic variables (age <50 or ≥ 50 years; gender; BMI <25, 25 to <30, or ≥ 30; medication use (yes/no) for benzodiazepine or benzodiazepine receptor agonist, tricyclic or serotonin–norepinephrine reuptake inhibitor antidepressants) were determined using χ^2 test for nominal/categorical variables and one-way analyses of variance for continuous variables. Differences in OSA classification between groups were analyzed using χ^2 test. Significance level was set at 0.05.

Sensitivity and specificity analyses were calculated to determine the ability of D/A ratios to predict fibromyalgia status. The receiver operative curves were plotted graphically for consecutive cutoff points calculated from the D/A ratio, from ≤1 or ≤11. These curves reflect the sensitivity of the cutoff point (0 = no fibromyalgia and 1 = fibromyalgia for lower values of the D/A ratio) against the false positive rate over all scores. The area under the receiver operator curve, which reflects the overall utility of the D/A ratio cutoffs, was calculated for each cutoff point; in general, the greater the area under the curve, the better the screening test at predicting fibromyalgia. The optimum cutoff is near the "shoulder" of the curve (Polit and Beck, 2008). Positive predictive value (PPV) and negative predictive value (NPV) for D/A ratio cutoffs were determined using contingency table values.

To determine potential effects of covariates on D/A ratios, nonparametric statistics were used based on number of levels within a non-continuous variable. For variables with two levels (gender, age, use of benzodiazepine or benzodiazepine receptor agonist, or

use of tricyclic or serotonin–norepinephrine reuptake inhibitor antidepressants), Mann–Whitney *U* tests allowed determination of mean ranks comparison. For variables with more than two levels (BMI), Kruskal–Wallis K served as the analysis of variance analog to determine differences between groups. When levels of a covariate were determined to potentially affect D/A ratio ($P < 0.05$), data were divided into two groups (persons with and without fibromyalgia), and nonparametric tests allowed determination of the effects of the covariate on D/A ratios by fibromyalgia status. Data analysis was performed using IBM SPSS Statistics 20.0.

RESULTS

Demographics

Of the 385 patients in the study population, 133 had fibromyalgia according to ACR criteria. The two subgroups, those with and without fibromyalgia, were similar in age and sleepiness, as measured with the Epworth Sleepiness Scale; however, they differed significantly in gender, medication use, and BMI (Table 1). The fibromyalgia group had a higher percentage of females as well as a higher utilization of benzodiazepines, benzodiazepine agonists, and antidepressants and had a lower BMI.

Polysomnography

Total Sleep Time differed significantly between the fibromyalgia and the non-fibromyalgia groups with Total Sleep Time of the fibromyalgia group averaging almost 40 minutes longer than that of the non-fibromyalgia group. Levels of OSA differed significantly between patients with and without fibromyalgia (Table 2). Although most patients with fibromyalgia did not have OSA, 45% met criteria for OSA. Most PSG measures did not differ significantly between the 2 groups, including Sleep Efficiency, Wake After Sleep Onset time, Apnea/Hypopnea Index, Respiratory Distress Index, all PLM measures, and Narcolepsy/Idiopathic Hypersomnolence (Table 1).

Delta/Alpha Ratio

The D/A ratio was calculated to be 13.3 overall with an SD value of 26.0 and a range of 0.3 to 231 (Table 1). Persons with fibromyalgia had lower D/A ratios than those without fibromyalgia (7.4 vs. 16.5, $P < 0.01$). Table 3 presents values for D/A ratio cutoff points from 1 through 11 and shows the sensitivity and specificity of the D/A ratio for fibromyalgia. A D/A ratio limit of ≤ 1 results in 95% specificity for fibromyalgia, whereas a D/A ratio limit of ≤ 10 results in 83% sensitivity for fibromyalgia. The highest area under the receiver operator curves are for D/A ratio cut points between 8 and 10.5, and sensitivities in this range were between 76% and 85%. The optimal cut point for sensitivity is D/A ratio ≤ 10.5. The PPVs (proportion of persons with an ACR diagnosis of fibromyalgia who would be classified as positive for fibromyalgia using the D/A cut point) for D/A ratios are moderate; for example, the proportion of persons with positive test results who would be correctly diagnosed (based on ACR criteria as the standard) is 54% with a D/A ratio ≤ 10.5. However, the NPV is moderately high at 89% (Table 3), indicating a high proportion of persons with negative test results (D/A ratio > 10.5) that would be correctly found not to have fibromyalgia. Analysis that considered OSA patients in both groups as well as excluding all Sleep Apnea patients in both groups was performed and did not produce a meaningful difference in sensitivity or specificity.

Further analyses were performed within the whole group looking at the D/A ratio according to age, gender, BMI category, and

TABLE 1. Sample Description (Frequency/Percentage or Mean/SD/Range)

Variable	Total Group ($N = 385$)	Persons With Fibromyalgia ($N = 133$)	Persons Without Fibromyalgia and Severe OSA ($N = 252$)
Demographic characteristics/health history			
Gender—male	142 (36.9%)	5 (3.8%)	137 (54.4%)**
Taking benzodiazepines or benzodiazepine agonist	97 (25.2%)	61 (45.9%)	36 (14.3%)**
Taking antidepressants (tricyclic or SNRIs)	100 (26.0%)	56 (43.6%)	42 (16.7%)**
Age, years	49.2 (12.8); 15–75	48.6 (11.1)	49.5 (13.6)
BMI	30.1 (6.4); 13.1–52.0	28.9 (5.9)	30.7 (6.6)*
Epworth Sleepiness Scale	10.5 (5.4); 0–26	10.4 (5.4); n = 131	10.5 (5.4); n = 251
Sleep variables			
Time spent sleeping†	279.3 (102.8); 59.0–550.0	304.6 (95.8)	265.9 (104.1)**
Sleep Efficiency, %	77.9 (14.2); 22.3–98.8	78.5 (12.6)	77.5 (15.2)
Wake After Sleep Onset, minutes	453.1 (44.2); 0–236	55.3 (42.5)	51.9 (45.1)
Apnea/Hypopnea Index†	10.2 (11.0); 0–80.2	9.4 (14.8)	10.7 (8.3)
Respiratory Distress Index†	14.6 (13.7); 0–94.7	13.1 (17.8); n = 132	15.4 (10.9)
PLM—yes	57 (14.8%)	16 (12.0%)	41 (16.3%)
Periodic Limb Movement Index	15.2 (18.3); 0.2–99.9	12.8 (13.7); n = 48	16.5 (20.3); n = 82
Periodic Limb Movement Arousal Index	9.3 (15.1); 0.1–83.9	6.8 (14.2); n = 52	10.8 (15.5); n = 89
Narcolepsy/Idiopathic Hypersomnolence	25 (6.5%)	10 (7.1%)	15 (6.0%)
Delta event/alpha event ratio†	13.3 (26.0); 0.3–231.0	7.4 (11.1)	16.5 (30.7)*; n = 251

Periodic Limb Movement Indices only include persons who have PLM and PLMA greater than 0.

Differences between persons with FM: *$P < 0.01$; **$P < 0.0001$.

†Levene's test indicates significant differences between groups in homogeneity of variances or non-normal distribution.

BMI, body mass index; OSA, obstructive sleep apnea; PLM, periodic limb movement; PLMA, periodic limb movement arousal; SNRI, serotonin–norepinephrine reuptake inhibitor.

TABLE 2. Obstructive Sleep Apnea Classification by Fibromyalgia Status

Apnea/Hypopnea Index Level	Persons with Fibromyalgia	Persons Without Fibromyalgia
None (<5)	73 (55%)	84 (33%)
Mild (5–15)	38 (29%)	86 (34%)
Moderate–severe (15+)	22 (17%)	82 (33%)
Total	133	252

χ^2 (2) = 19.00, $P < 0.001$.

medication use (Table 5). Significant differences were found for age (15–50 years and 51–75 years), BMI (<25, 25–30, and >30), and use of benzodiazepines or benzodiazepine agonist (yes/no). Further analysis based on fibromyalgia status indicated that differences in age were significant only in persons without fibromyalgia (younger persons had higher mean ranks than older). Among those using benzodiazepines and benzodiazepine agonists, the D/A was significantly reduced for both those with fibromyalgia and those without fibromyalgia, indicating a medication effect that is independent to fibromyalgia status; however, those with fibromyalgia who were not using a benzodiazepine or benzodiazepine agonist had lower D/A than those without fibromyalgia, indicating that fibromyalgia reduced D/A regardless of benzodiazepine use. On average, the D/A ratio was lower in the fibromyalgia group not using benzodiazepines compared with the non-fibromyalgia group using benzodiazepines (Fig. 1).

Because of the significant difference found with use of benzodiazepine and benzodiazepine agonists, sensitivities, specificities, and PPV/NPV were calculated for the group not taking these agents (Table 4). The optimal area under the curve continued to be cutoffs between 8 and 11 (0.573–0.587). Interestingly, PPV ranges were higher (from 69% to 78% in the D/A cutoff range of 8–11), supporting the probability that fibromyalgia is present when the D/A cutoff is in this range. There were also lower NPVs (ranges from 37% to 48% with D/A cutoffs 8–11) when the analysis only contained persons not taking benzodiazepines or benzodiazepine agonists.

For gender, there was a trend toward a difference in the average D/A ratio for the entire sample ($P = 0.061$). Neither group (with or without fibromyalgia) showed significant differences in D/A ratio according to gender, although scrutiny of the mean ranks indicates that the small number of males with fibromyalgia had a higher mean rank than women with fibromyalgia, the lack of significance of the test probably reflects the uneven cell numbers. No difference was found in the whole group based on use of antidepressants.

DISCUSSION

The diagnosis of fibromyalgia is most often based on the 1990 ACR criteria, which include both subjective criteria of pain and Manual Tender Point Examination findings. The 2010 criteria proposed by the ACR are based more fully on subjective responses and do not rely on physical examination (Wolfe et al., 1990, 2010). The dependence of both sets of criteria on clinical features is due to the absence of a generally accepted laboratory measures for fibromyalgia, which has resulted in concerns about diagnostic accuracy. Our analysis has shown that a low D/A ratio measured by qEEG on routine PSG can have both high sensitivity and specificity for fibromyalgia.

Sleep Measures and Fibromyalgia

Fatigue and nonrestorative sleep are the most commonly reported symptoms by patients with fibromyalgia; however, the cause for these problems is not well understood, and the routine PSG features in fibromyalgia are not well established (Bennett et al., 2007). Sleep-disordered breathing was common in the fibromyalgia group with 45% meeting criteria for OSA, and 17% having an Apnea/Hypopnea Index >15, which is significantly higher than the 2% to 7% prevalence of OSA in the general population (Lurie, 2011; Young et al., 1993). An increased incidence of sleep-disordered breathing in fibromyalgia patients is consistent with previously published smaller studies (Germanowicz et al., 2006). With a higher prevalence of OSA in persons with fibromyalgia than in persons in the general population, the diagnosis of fibromyalgia may suggest a need to consider OSA and PSG for comprehensive patient care. Fibromyalgia is often thought to co-occur with both restless leg syndrome and PLM disorder (Viola-Saltzman et al., 2010). In our sample of persons referred for sleep studies, the prevalence of PLM/PLM with arousals was 12% in fibromyalgia patients, which was not significantly different from the non-fibromyalgia group (16%).

A higher than expected number of fibromyalgia patients met criteria for clinically significant hypersomnolent syndromes. The incidence of narcolepsy is thought to be approximately 1 in 2000 or 0.5% of the population, and idiopathic hypersomnolence is thought to be present in less than 5% of population (Billiard, 1996). In this study, 7.1% of fibromyalgia patients met criteria for

TABLE 3. Sensitivity, Specificity, and Predictive Calculations at Cut Points for D/A Ratios From ≤1 to ≤11 for Total Study Group (n = 385)

	1	2	3	4	5	6	7	8	9	10	10.5	11
Sensitivity	0.083	0.248	0.301	0.380	0.594	0.654	0.714	0.759	0.782	0.827	0.850	0.850
Specificity	0.948	0.865	0.699	0.610	0.583	0.540	0.476	0.544	0.579	0.607	0.623	0.647
Area under the ROC curve	0.515	0.556	0.568	0.575	0.588	0.594	0.596	0.600	0.600	0.602	0.612	0.600
PPV	0.458	0.493	0.448	0.434	0.429	0.429	0.419	0.468	0.495	0.526	0.543	0.559
NPV	0.661	0.686	0.699	0.711	0.731	0.747	0.759	0.811	0.834	0.869	0.887	0.891

Prevalence of FM (ACR criteria) 35% in 385 cases. PPV = proportion of persons with positive test results (D/A ratio) who are correctly diagnosed (based on ACR as gold standard). NPV = proportion of persons with a negative test result (D/A ratio) who are correctly diagnosed (based on ACR as gold standard).

ACR, American College of Rheumatology; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating curve.

TABLE 4. Sensitivity, Specificity, and Predictive Calculations at Cut Points for D/A Ratios From ≤1 to ≤11 for Subgroup Not Using Benzodiazepines or Benzodiazepine Agonists (n = 278)

	1	2	3	4	5	6	7	8	9	10	10.5	11
Sensitivity	0.003	0.371	0.279	0.283	0.297	0.293	0.300	0.309	0.297	0.298	0.300	0.292
Specificity	0.639	0.767	0.759	0.765	0.782	0.787	0.806	0.825	0.819	0.832	0.842	0.833
Area under the ROC curve	0.498	0.539	0.518	0.527	0.550	0.552	0.568	0.587	0.573	0.580	0.584	0.573
PPV	0.004	0.181	0.264	0.361	0.481	0.542	0.639	0.694	0.708	0.750	0.778	0.778
NPV	0.565	0.899	0.773	0.694	0.616	0.565	0.500	0.482	0.440	0.412	0.394	0.370

Prevalence of FM (ACR criteria) 25% in 287 cases. PPV = proportion of persons with positive test results (D/A ratio) who are correctly diagnosed (based on ACR as gold standard). NPV = proportion of persons with a negative test result (D/A ratio) who are correctly diagnosed (based on ACR as gold standard).

ACR, American College of Rheumatology; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating curve.

hypersomnolence, which may represent a greater than 50% increase in hypersomnolent conditions compared with the general population.

Alpha Intrusions on EEG

Although alpha intrusions into slow-wave sleep have been associated with fibromyalgia since 1975 (Roizenblatt et al., 2001), there still is no generally accepted method to quantify this finding or use it as a diagnostic test. Advances and more widespread use of qEEG analysis provide an opportunity to use this technique to fill a diagnostic gap by objectively and reliably determining alpha and delta powers for individual patients. This approach does not require subjective scoring of EEG activity. The D/A, as determined by qEEG, can be both sensitive and specific for the diagnosis of fibromyalgia and can have a high PPV and NPV. The benefit of the D/A is not always its specificity. In a general population, the specificity at the optimal cutoff value (10.5) is a modest 62%, but the high NPV (89%) in the general sleep disorder population can assist clinicians in eliminating or ruling out fibromyalgia as a potential diagnosis. With the often heterogeneous and difficult to diagnose presentation of fibromyalgia, the high NPV may be useful. In a population not using benzodiazepines or benzodiazepine agonists, the specificity is greater and is between 83% and 84% at the optimal cutoff. The corresponding PPV in the subject population is between 69% and 78%.

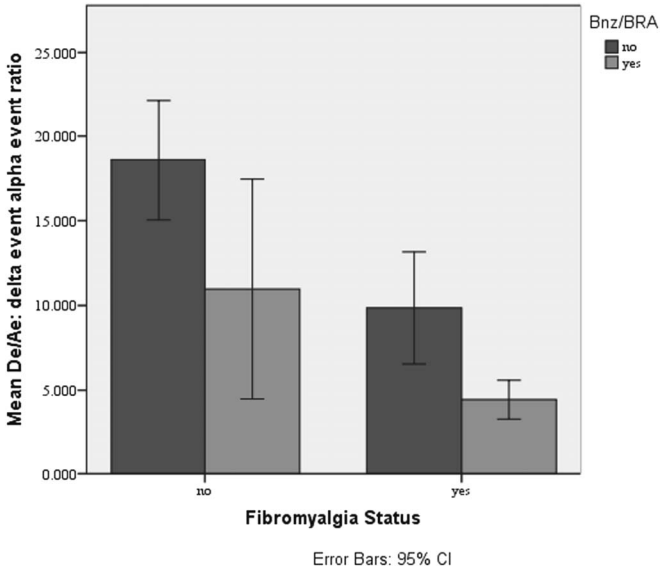

FIG. 1. D/A ratio according to use of benzodiazepines or benzodiazepine agonists in patients with and without fibromyalgia (status no/use no: $n = 215$, status no/use yes: $n = 36$, status yes/use no: $n = 72$, status yes/use yes: $n = 61$).

Several factors were found to be associated with D/A in our population (Table 5). Those found significantly associated with lower D/A ratios in our total sample were higher age, lower BMI, and use of benzodiazepines or benzodiazepine agonists. Among those with fibromyalgia, only age and use of benzodiazepines or benzodiazepine agonists were significantly associated with D/A ratios. In contrast, using benzodiazepines or benzodiazepine agonists was the only significant result in those without fibromyalgia. The trend effect of gender on D/A is difficult to interpret because of the small number of men in our sample. Studies with larger proportions of men are needed to test this association.

Alpha Intrusions and Pain

Alpha intrusions into slow-wave sleep may represent a form of nonrestorative sleep and are not specific to fibromyalgia. Alpha intrusions are present in other pain disorders and also in affective disorders, insomnia, sleep-disordered breathing, and some movement disorders (Manu et al., 1994). Although there is a correlation between slow-wave sleep abnormalities and the experience of nonrestorative sleep and chronic pain, there is no clear cause-and-effect relationship. Pain clearly can affect sleep, but deep sleep deprivation also increases pain perception as shown by slow-wave sleep deprivation studies in young healthy individuals (Moldofsky and Scarisbrick, 1976). In a review, Moldofsky reported studies supporting disordered sleep physiology as causing generalized myalgia; in general, disturbances to slow wave or deep sleep produce generalized hyperalgesia (Moldofsky, 2008). Further study is needed to elucidate the interrelationship of dysfunctional sleep and chronic pain.

Tonic and Phasic Alpha

The symptoms of fibromyalgia have been correlated with different types of alpha activity during sleep, as identified with nonquantitative methods (Roizenblatt et al., 2001). Phasic alpha intrusion has been more highly correlated to increased pain after sleep and reports of poor sleep than tonic alpha. Further analyses would be required to assess if subpatterns of qEEG used in this trial correlate with specific clinical symptoms, as have been described with non-qEEG techniques previously described.

TABLE 5. Effects of Gender, Medication Usage, and Age on D/A Ratios

	Total Sample			Persons With Fibromyalgia			Persons Without Fibromyalgia		
	N	Mean Rank	*P*	*N*	Mean Rank	*P*	*N*	Mean Rank	*P*
Gender									
Men	142	206.36	0.061	5	84.60	0.298	137	123.82	0.602
Women	242	184.37		128	66.31		114	128.62	
Age, years									
15–50	195	209.54	0.002	71	69.07	0.507	124	142.27	<0.0001
51–75	189	174.92		62	64.63		127	110.12	
BMI									
<25	72	167.83	0.024	29	60.02	0.194	43	111.42	0.259
25–30	154	187.00		58	64.11		96	124.77	
30+	158	209.10		46	75.04		112	132.67	
Benzodiazepines or benzodiazepine agonist									
Yes	97	138.93	<0.0001	61	54.02	<0.0001	36	94.14	0.004
No	287	210.88		72	78.00		215	131.33	
Antidepressants (tricyclic or SNRIs)									
Yes	100	185.40	0.457						
No	284	195.00							

Differences determined by nonparametric analyses.
BMI, body mass index; SNRI, serotonin–norepinephrine reuptake inhibitor.

Implications for Treatment

With replicated evidence that alpha intrusions into slow-wave sleep are associated with diffuse pain and may reflect a cause for pain through sleep dysfunction, interventions that affect slow-wave sleep have been evaluated for impact on pain. Of the Food and Drug Administration-approved medications for fibromyalgia, duloxetine and milnacipran, which are both serotonin–norepinephrine reuptake inhibitors, may interfere with sleep and have been noted to worsen symptoms such as restless leg syndrome and PLM (Rottach et al., 2008). Pregabalin, which is an alpha-2 ligand, has been shown to reduce sleep complaints and may also improve slow-wave sleep (Hindmarch et al., 2005; Russell et al., 2009b). Sodium oxybate, an endogenous neurotransmitter that is an active irreversible agonist of the GABA-B subtype receptor, significantly increases slow-wave sleep and reduces alpha intrusions as well as improving growth hormone levels (Scharf et al., 2003). In a large randomized, controlled, double-blind trial for fibromyalgia, sodium oxybate significantly reduced pain and fatigue and improved quality of sleep (Russell et al., 2009a). The improvement of alpha intrusions and the extent of pain, as shown through an interventional trial in patients with fibromyalgia with the use of sodium oxybate, support the potential use of D/A ratio as a disease severity marker, in addition to our quantification in this study of its utility as a diagnostic marker (Rosenfeld et al., 2010).

Strengths and Limitations

This study represents the largest consecutive series of patients with fibromyalgia who were referred to a single community-based laboratory for PSG. The large sample size and determination of pain symptoms and PSG measures for every patient has allowed differentiation of multiple sleep characteristics based on fibromyalgia status. The consistency in the evaluation is related to the use of a single community-based sleep medicine center for subject inclusion. This referral pattern and common procedure are both a strength and limitation. They allowed for systematic and standardized approaches across the entire patient population but also potentially decreased the generalizability to other populations. Furthermore, only patients being referred for PSG for typical clinical indications were included, and the patients with and without fibromyalgia were not matched, so additional investigation is needed to compare the qEEG results to persons with and without fibromyalgia without suspected sleep disorders. Although the D/A results may be useful in its sensitivity or specificity, it may be more helpful in ruling out rather than diagnosing fibromyalgia given its high NPV. Its use to rule in fibromyalgia is more limited because of the effect of benzodiazepines and benzodiazepine agonists. Further study will be required to reproduce the validity of the D/A as a marker for fibromyalgia. Finally, although PSG is a routine diagnostic test that is readily available, it requires a full night of testing, and thus, it may not be acceptable to some patients. Among methodological limitations, the cutoff for delta frequency was 1 Hz, which disallowed capture of lower frequency delta waves, and monitoring of D/A changes over sleep cycles and by specific EEG electrodes was not possible, and this might possibly improve D/A sensitivity and specificity.

CONCLUSIONS

Polysomnography can be used to identify common sleep disorders in the fibromyalgia population such as sleep-disordered breathing and hypersomnolence. With qEEG, conventional PSG is a readily available means to identify the ratio of delta to alpha activity during non-REM sleep, and this D/A ratio can be a reliable

marker of fibromyalgia. However, benzodiazepine and benzodiazepine agonist use should be considered when interpreting D/A as a specific marker for fibromyalgia. Nevertheless, D/A may be an objective supplementary marker of fibromyalgia diagnosis, especially to reduce the likelihood of misdiagnosis.

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