ELSEVIER

Sleep Medicine 1 (2000) 195–207

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Review

Nighttime sleep and daytime functioning (sleepiness and fatigue) in less well-defined chronic rheumatic diseases with particular reference to the 'alpha-delta NREM sleep anomaly'

Maren L. Mahowald[a,*], Mark W. Mahowald[b, c]

[a]*Department of Medicine, Minneapolis Veteran's Administration Medical Center, University of Minnesota Medical School, Minneapolis, MN, USA*

[b]*Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, Minneapolis, MN, USA*

[c]*Department of Neurology, University of Minnesota Medical School, Minneapolis, MN, USA*

Received 9 March 2000; received in revised form 23 March 2000; accepted 24 March 2000

Abstract

For the past 25 years, the 'alpha-delta NREM sleep abnormality' has been used by some as a defining or legitimizing marker for poorly defined rheumatic diseases such as fibromyalgia and chronic fatigue syndrome. Comprehensive review of the literature reveals no support for such a conclusion. Most studies involve small numbers of patients. The lack of control subjects, non-standardized recording techniques, and confusion between tonic and phasic alpha frequency activity patterns make comparison difficult. There is much evidence that this sleep EEG pattern is not only non-specific, but may actually reflect a sleep maintaining process. The 'sleep fragmentation' theory of the complaint of non-restorative sleep in this patient population is invalidated by the fact that conditions characterized by severe sleep fragmentation, such as obstructive sleep apnea, are not associated with musculoskeletal symtoms. It is difficult to attribute musculoskeletal symptoms to disorders of sleep in view of the fact that the only organ of the body known to benefit from sleep, or to be adversely affected by lack of sleep, is the brain. It is concluded that fibromyalgia and chronic fatigue syndrome are associated with subjective sleep complaints, but do not represent sleep disorders.

Keywords: Fibromyalgia; Chronic fatigue syndrome; Sleep; Alpha-delta sleep; Alpha-delta NREM sleep anomaly; Musculoskeletal pain

1. Introduction

Over the past 25 years, a purported relationship between a specific sleep EEG pattern, termed 'alpha-delta sleep EEG' pattern, or the 'alpha NREM sleep anomaly' and certain non-articular rheumatic conditions has been suggested. There has been the temptation to use this sleep EEG pattern as a defining or legitimizing objective laboratory finding for these conditions – primarily fibromyalgia (FM) and its closely-related condition, the chronic fatigue syndrome (CFS). The purpose of this review is to place these relationships in perspective, and to call for more rigorous scientific study.

2. Fibromyalgia

The fibromyalgia syndrome (FM) (fibrositis) (rheumatic pain modulation disorder) is a non-articular

* Corresponding author 1 Veteran's Drive, Minneapolis, MN 55417, USA. Tel.: +1-612-725-2000.

E-mail address: mahow001@tc.umn.edu (M.L. Mahowald).

1389-9457/00/$ - see front matter
PII: S1389-9457(00)00028-9

rheumatic condition characterized by complaints of pain, stiffness, disturbed or non-restorative sleep, and fatigue. Despite its reportedly high prevalence, FM lacks documented pathologic basis and confirmatory laboratory findings [1,2]. Its legitimacy as a diagnosis has been questioned [3–8]. The primary physical finding is 'tender points' [1,9,10]. Subjective 'sleep disturbance' (insomnia and/or 'non-restorative' sleep) is reported by 60–90% of FM patients [11,12]. The alpha-delta sleep EEG pattern has been said to be highly correlated with FM, promoting the thesis that this EEG sleep pattern defines or legitimizes this condition.

A recently-advanced theory of the etiology of FM is based upon the 'restorative function' of sleep, and proposes a combination of factors including deprivation of slow wave sleep (SWS) and poor physical fitness [13]. The reduction in SWS is postulated to be an effect of reduction in exercise. In fact, physiologic studies have demonstrated that the association between exercise and SWS is solely dependent upon exercise-induced change in body temperature, and is, in fact independent of and unrelated to exercise (or conditioning) per se. SWS can be enhanced by increasing body temperature without exercise, and this enhancement can be prevented by keeping body temperature constant during exercise [14,15]. Furthermore, the percentage of SWS in patients with FM and CFS is normal [16–18].

3. Chronic fatigue syndrome

Recently, it has been suggested that FM may bear some relationship to CFS [16,19,20]. As with FM, patients with CFS complain of fatigue [21], but objective sleep studies are rare: the majority had insomnia, but their sleep (including total sleep time) was otherwise normal. Regrettably, extremity movements were not monitored, and objective studies of daytime sleepiness were not performed [22,23]. A shortened latency to REM sleep at night (thought to be a marker for depression) correlated with the degree of depression in one group of CFS patients [24].

'More alpha EEG sleep' was found in all of ten subjects in one report of CFS [17], but the alpha-delta sleep EEG pattern was found in none of six in another series [25]. Not all studies have identified the alpha-delta sleep EEG pattern in this patient population [26].

It must be remembered that true excessive daytime sleepiness due to underlying primary sleep disorders such as obstructive sleep apnea or narcolepsy may masquerade as either FM or CFS [27].

The entire issue of 'restorative' or 'non-restorative' sleep with regard to musculoskeletal pain and/or fatigue syndromes becomes problematic in view of the fact that the only organ system of the body known to benefit from sleep is the brain [28].

4. Non-specificity of the alpha-delta sleep EEG pattern

The alpha-delta sleep EEG pattern was first reported by Hauri and Hawkins in a group of nine patients (eight with psychiatric disorders and one normal), and was defined as the presence of alpha and delta waves during stage 2 sleep [29]. It was never designated as the alpha-delta sleep EEG pattern if enough delta activity was present to score stage 3 sleep. Virtually all subsequent references to the alpha-delta sleep EEG refer to alpha frequency EEG activity in stages 3/4 NREM sleep. Later, Moldofsky reported the presence of alpha frequency activity in stages 2, 3, and 4 of NREM sleep in seven of ten patients with fibrositis. In a subsequent study of six normal subjects, he experimentally induced alpha frequency EEG intrusions into stage 4 sleep by delivering an auditory stimulus, resulting in a reported increase in musculoskeletal symptoms [30]. The similarity of this experimentally-induced transient (phasic) alpha pattern to the more static spontaneous (tonic) alpha frequency EEG activity observed in the fibrositis patients prompted the theory that the alpha-delta sleep EEG pattern represented fragmented, and therefore, 'non-restorative' sleep [31]. It is important to note that these early studies were not controlled. A recent study of slow wave sleep interruption on pain thresholds and fibromyalgia-like symptoms in healthy subjects failed to replicate the earlier, exclusively quoted study [32]. Conversely, another suggested that slow wave sleep disruption could reduce pain threshold and increase fatigue. Notably, this study did not find an increase in the alpha-delta sleep EEG pattern [33].

Further underscoring its non-specific nature, the alpha-delta sleep EEG pattern was found in 9% of 434 patients studied for the complaint of excessive daytime sleepiness [34]. Scheuler et al. found this pattern in 15% of 240 normal subjects [35] where there was a suggestion of a familial tendency. In that study, the alpha-delta sleep EEG pattern occurred more frequently in persons with *undisturbed* sleep (20.5%) than in persons with sleep disturbances (8.3%) [35–37]. Sixteen of his normal subjects with the alpha-delta sleep EEG pattern were compared to an equal number of matched controls. There were fewer phasic events (which might suggest arousal) in those with the tonic alpha-delta sleep EEG pattern. He concluded these individuals seem to have more consolidated sleep, and the alpha-delta sleep EEG pattern is not indicative of an arousal disorder or a more highly activated state as was likely the case in auditory stimulus-induced phasic alpha frequency activity [30,38]. Importantly, Moldofsky reported that in a group of patients with osteoarthritis, the alpha-delta sleep EEG pattern was seen with equal frequency in those with and without complaints of morning symptoms [39]. The variability of the presence of the alpha-delta sleep EEG pattern in different groups of patients with FM indicates the tenuous relationship between the alpha-delta sleep EEG pattern and FM [40,41].

5. Tonic vs. phasic alpha frequency activity

When considering EEG changes in specific disease groups, care must be taken not to confuse the two very different types of alpha-delta sleep EEG patterns. The alpha-delta sleep EEG pattern described by Hauri and Hawkins is tonic- more or less continuously riding upon the background of non-REM sleep (as might be seen if they were a state/trait marker). The alpha-delta sleep EEG pattern of alpha frequency intrusions appears phasically (intermittently) as an arousal response to exogenous stimuli such as auditory tones or to endogenous arousals as seen with obstructive apneic events or with periodic extremity movements. The nominal similarity of experimentally-induced arousals with phasic alpha frequency intrusion pattern to the more tonic, spontaneously appearing tonic alpha-delta sleep EEG pattern prompted the hypothesis that the spontaneous tonic alpha-delta sleep EEG pattern represented arousal disorder with fragmented sleep which was 'non-restorative' in fibrositis patients [42]. It is important to note that these early studies involved few subjects and were not controlled.

The important distinction between 'phasic' and 'tonic' alpha-delta sleep EEG patterns was not made in the PSG-based studies of sleep in FM. Moreover, many of the studies were performed without respiratory or extremity movement monitoring, raising the possibility that induced, or phasic, alpha-delta sleep EEG pattern was associated with sleep-disordered breathing or with extremity movements.

Further confusing the issue of tonic and phasic alpha frequency EEG activity during sleep is the 'periodic K-alpha sleep' pattern. This pattern has been associated with complaints of 'unrefreshing sleep' [43] but appears to be indistinguishable from the cyclic alternating pattern, which is a normal physiologic sleep phenomenon [44–46].

One important, but consistently ignored fact is that the EEG electrode montage employed will change the amount of alpha frequency EEG activity [26]. It is likely that alpha frequency activity during NREM sleep may represent different phenomena which may be identifiable by periodicity analysis [47] (Figs. 1 and 2).

If fragmentation of SWS, associated with 'alpha intrusion' into NREM sleep in fact leads to FM-like symptoms, then most patients with OSA, whose sleep is fragmented hundreds of times nightly, often with alpha frequency intrusion into sleep attendant with the endogenous arousals, could be expected to have FM symptoms. This has been addressed in a number of studies. May et al. [48] screened all new fibromyalgia patients in one rheumatology clinic for suspicion of sleep apnea. Four of 92 women, and 13 of 25 men with the new diagnosis of FM underwent PSG studies. Two out of 92 (2.2%) women and 11 out of 25 (44%) men had significant sleep apnea. It was concluded that sleep apnea is not a significant cause of FM in women, and that FM may be a marker for sleep apnea in men. The mean apnea-hypopnea index was only 12 in the women, and only 18 in the men. The alpha-delta sleep EEG pattern was seen in six of the 11 men, and not commented upon in the women [48]. In a larger study, only 2.2% of 108 patients attending a respiratory sleep

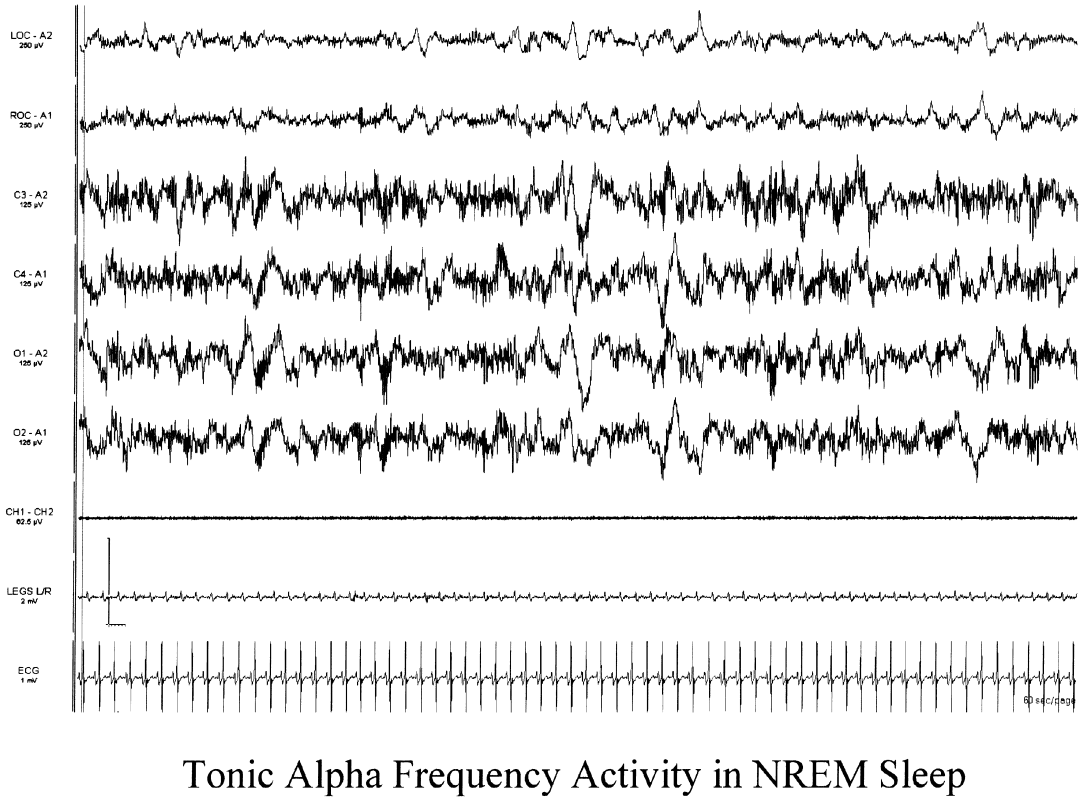

Fig. 1. Tonic alpha-delta NREM sleep pattern. The alpha frequency activity is widely distributed and present throughout the epoch.

disorders clinic had symptoms of FM (this is equal to or less than the reported prevalence of FM in the general population) [49]. A 3% prevalence was found in another study of 30 patients with OSA with a respiratory disturbance index of 30/h. The study of Molony et. al. indicating symptoms of FM in 3/11 men with OSA is difficult to evaluate, as the inclusionary criterion for the diagnosis of OSA was an apnea index of 2/h, which is normal [50]. The striking lack of FM symptoms in patients with OSA is a major challenge to the sleep fragmentation theory as a cause of musculoskeletal or fatigue symptoms.

Table 1 lists polysomnographic studies mentioning 'alpha-delta sleep EEG' sleep in patients with FM, CFS, and other rheumatologic conditions.

Therefore, the alpha-delta sleep EEG pattern has been reported both in rheumatologic disorders, and in a wide variety of conditions, many of which have been associated with neither pain nor rheumatologic disorders [51–58]. Despite this, the alpha-delta sleep EEG pattern continues to be cited as a physiologic basis of, or marker for, the 'fibrositis' syndrome [59].

6. Alpha frequency activity as a 'sleep maintaining' process

Although it is commonly assumed that the presence of alpha frequency EEG activity during SWS implies arousal or diminished depth of sleep, some studies conclude the opposite, that this alpha frequency activity is a manifestation of a physiological phenomenon of sleep [60] and may even represent a heightened level of sleep depth [35,55]. Pivik's study concluded: '...existing data – including defining electrophysiological characteristics, topographic distribution and state and behavioral correlates ' provide a compelling argument that the EEG activity identified with the alpha-delta sleep EEG pattern does not primarily represent arousal-associated occipital alpha activity,

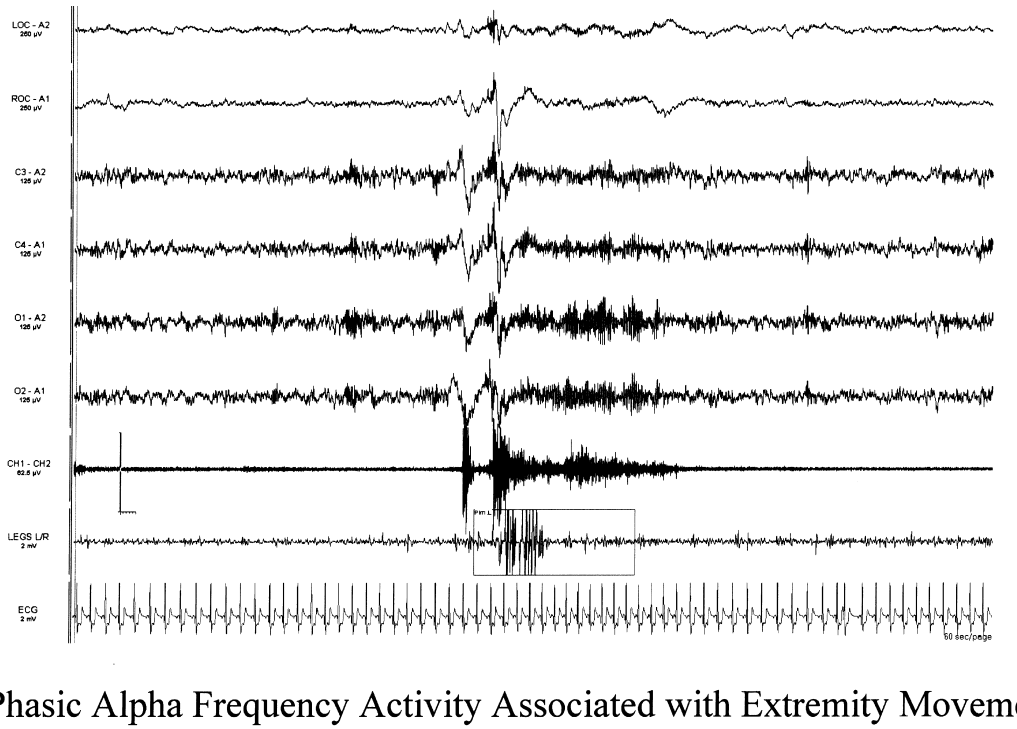

Fig. 2. Phasic alpha frequency activity. Note the phasic nature of the posteriorly predominant alpha frequency activity associated with an extremity movement – the same type of phasic activity induced by auditory stimuli administered during NREM sleep.

but reflects a fronto-central alpha which not only does not constitute the arousing, sleep disturbing influence commonly attributed to it, but is associated with sleep-maintaining processes' [61].

7. Summary and future directions

In the context of the evolving understanding of the alpha-delta sleep EEG pattern, it becomes clear, as is true with many 'diagnostic finds', initial reports of striking sensitivity and/or specificity of tests in clinical disorders may fall short with expanded study of larger numbers of patients and populations. The very nature, and even the existence, of FM and CFS continue to be questioned [3,5–7,62,63]. Certainly, the alpha-delta sleep EEG pattern falls short of a legitimizing 'finding' in this controversy. Van Sweden's conclusion that 'alpha-delta or alpha-sleep is still an atypical and aspecific sleep pattern with an unclear pathophysiology' is well-stated [64].

This systematic review of the literature conclusively demonstrates that the alpha-delta sleep EEG pattern is extremely non-specific: it may occur in normal individuals, possibly as a genetically-determined pattern, and in a wide variety of conditions associated with neither musculoskeletal symptoms nor complaints of fatigue. Conversely, this pattern is often not present in patients with FM or CFS. The absence of musculoskeletal symptoms in patients with conditions associated with severe sleep fragmentation (such as OSA) is compelling evidence that the musculoskeletal or fatigue symptoms of FM or CFS are not due to disrupted sleep. This fact is supported by the normal sleep architecture reported in most studies of patients with FM and CFS, and the absence of even a single study documenting objective excessive daytime sleepiness in these conditions. Further studies in this area must be performed with great standardization of recording techniques. Age and sex-matched controls are mandatory, as are objective measurements of daytime sleepiness.

Table 1
Objective studies of alpha-delta NREM sleep (A-D) in various clinical conditions and normal controls

Reference	Nature of study	A-D findings, comments
Moldofsky et al., 1975 [30]	2-part study: Part 1: 10 patients with FM; 7/10 FM patients had tonic A-D sleep. Only difference from literature controls was increase in Stage 1 sleep; Patients subjectively reported increased muscular pain and stiffness in am. Part 2: 6 normal volunteers – 3 nights of stage 4 sleep deprivation by auditory stimuli; Volunteers – reduced stage 4 sleep fragmented by phasic stimulus-induced alpha frequency activity; Volunteers demonstrated increased dolorimeter score on the first deprivation night	7/10 FM patients had tonic A-D sleep. Patients had tonic A-D sleep. The auditory-induced stage 4 sleep deprivation subjects had phasic A-D sleep. No controls
Moldofsky and Scarisbrick, 1976 [31]	Stage 4 and REM deprivation. 6 normal volunteers (same data from 1975 study) for Stage 4 deprivation; 7 normal volunteers for REM deprivation; REM deprivation: reduced REM sleep	All normal subjects; Stage 4 deprivation: Same data as 1975 study. REM deprivation: 4 showed decrease in muscle tenderness, 3 showed an increase. The only difference between these two studies is the addition of the REM deprivation group. The data for the stage 4 deprivation group are identical
Moldofsky and Lue, 1980 [65]	15 FM patients: 7 received l-tryptophan, 8 received chlorpromazine; Mean alpha and delta frequencies/min and mean alpha and delta power/min were measured in last 8 patients studied. No data regarding alpha are provided	Mean percentage time/min or mean percentage power/min of alpha frequency during NREM and REM sleep correlated with overnight increase in pain measures, hostility, and decrease in energy; No numerical data provided; No controls. No alpha time or power data are provided
Moldofsky et al., 1983 [57]	Ambulatory 4-channel PSG study of 15 patients with RA during acute flare	Alpha EEG sleep pattern found in all patients. Criteria not specified. No controls. No monitoring of respiration or anterior tibialis EMG
Moldofsky et al., 1984 [66]	9 patients with FM and sleep-related myoclonus and 9 patients without FM with excessive daytime sleepiness and sleep-related myoclonus; Sleep stage changes were significantly more frequent in the fibrositis group. No other sleep architecture differences were noted. Alpha EEG activity not commented upon	A/D not commented upon. Excessive daytime sleepiness measured by subjective sleepiness scales (no MSLT); The PSG figure clearly demonstrated phasic alpha intrusion associated with the leg movements
Moldofsky et al., 1986 [67]	33 patients with FM divided into two groups: 12 with sleep-related myoclonus; 21 without sleep-related myoclonus; Those with myoclonus were older, had later onset of illness, showed disrupted sleep with periodic involuntary leg movements that were related to fatigue, and alpha EEG sleep related to fatigue and pain	Alpha EEG rating for those without myoclonus was 2.54, for those with myoclonus was 2.63. Score 2.54 (0.43) in patients with FM without myoclonus and (2.63) (1.0) in patients with FM and myoclonus. No controls. The clinical significance of periodic limb movements of sleep is questionable. Some of same patients as reported in 1984 study?
Saskin and Moldofsky, 1986 [68]	11 female patients with FM and 11 female postaccident patients. Both groups had similar musculoskeletal pain, fatigue, sleepiness and A-D sleep. No difference in sleep architecture between the groups	The alpha EEG NREM anomaly was present in all of FM group and in 10/11 of postaccident group (no data provided). Score 2.5 (0.4) in FM patients, 1.8 (1.0) in postaccident patients ($P < 0.05$). No controls
Gupta and Moldofsky, 1986 [18]	6 patients with FM and 6 with dysthymic disorder. Concluded that FM and dysthymia are separate clinical entities	The 'alpha rating' (0–4 scale) was 2.5 (0.25) in FM patients, and 1.04 (0.44) in dysthymic patients. The 6 FM are probably 6 of the 10 originally reported in 1975. The 'theta burst' EEG pattern observed in the dysthymic patients has never been established as significant in any condition. No normal controls

Table 1 (*continued*)

Reference	Nature of study	A-D findings, comments
Fry et al., 1987 [34]	432 consecutive patients undergoing PSG evaluation for the complaint of excessive daytime sleepiness	The alpha-delta sleep pattern was found in 8.9% of all studies, representing a wide variety of disorders of excessive daytime sleepiness. Abstract
Moldofsky et al., 1987 [39]	PSG study of sleep in 8 patients with OA and 7 normal controls	Both groups had similar alpha NREM ratings (The control group had A-D rating (0–4) of 2.0 (1.0), which is considerably higher than in some control groups in FM studies)
Touchon et al., 1986 [69]	PSG study of 12 FM patients (7 female, 5 male) and 20 controls matched for age and sex	Alpha-delta sleep pattern noted in all patients, in none of controls. Criteria for determination of alpha-delta sleep not provided
Moldofsky et al., 1988 [16]	PSG study of 9 patients with FM secondary to a febrile illness, 9 patients with FM not related to a febrile illness, and 10 healthy controls	No difference in sleep architecture among the 3 groups. The two FM patient groups demonstrated A-D sleep (0–4) (with infection 1.9 (0.8); without infection 2.4 (0.7); controls 0.9 (0.9)
Crosby, 1989 [70]	PSG study of 15 patients with RA and 12 control subjects	'Alpha activity integrated within stage 2 sleep' was present in one RA patient and in two controls
Silva et al., 1991 [71]	PSG study of 8 FM patients	Alpha-delta sleep was present in 2/8; No mention of criteria for 'alpha-delta' sleep. No controls
Anch et al., 1991 [72]	12 FM patients and 13 controls	FM patients had less % stage 1 NREM and more REM sleep. Alpha ratings (1–4) were significantly higher in FM patients (2.4) than in controls (1.8)
Reynolds et al., 1991 [73]	Double blind, placebo control crossover design study of sleep, pain, fatigue, and mood symptoms in 12 patients with FM treated with cyclobenzaprine. 9 completed study	Mean baseline and washout alpha-non-REM score (0-–4) 1.9 (0.7); Baseline & washout (0–4): 1.9 (0.7); Placebo (0–4): 2.0 (0.9); No controls
Horne and Schackell, 1991 [41]	11 patients with FM and 15 normal controls. The mean percentage of NREM alpha-like activity in sleep was greater for the FM group, but not significantly different from controls	The overlap in distribution of NREM alpha-like activity between the two groups indicted that it is not directly related to musculoskeletal symptoms
Whelton and Moldofsky [74]	PSG study of 14 CFS patients and 12 controls. All CFS patients described unrefreshing sleep, but were not hypersomnolent by multiple sleep latency test	Alpha NREM scores (0–4) in CSF patients 2.2 (1.0) and controls 1.2 (1.0). Concluded that similarity of sleep complaints and A-D sleep pattern linked FM with CFS
Morriss et al., 1993 [75]	PSG study of 12 CFS patients and 12 controls. CFS patients had a reduced sleep efficiency, but greater total sleep time	No difference in A-D sleep. No respiratory or extremity EMG monitoring
Moldofsky et al., 1993 [76]	24 patients with posttraumatic FM were studied. Divided into two groups: those with and without litigation resolution	Alpha NREM scores (0–4) in resolved group (8 patients) 2.2 (0.9) and unresolved group (16 patients) 1.9 (0.5); No controls
Doherty and Smith, 1993 [77]	10 patients with FM and 10 with osteoarthritis	All patients reported 'disturbed sleep'. Alpha delta intrusion by visual and automated assessment was not identified in any patient
Hirsch et al., 1994 [78]	PSG and MSLT study of 19 patients with RA and 19 controls	The overall sleep architecture was preserved, but the RA patients had severe sleep fragmentation. Alpha-delta sleep was found in 6/19 and 'pathologic K-alpha complexes' were present in 6/19. No mention of these findings in the control group
Manu et al., 1994 [79]	PSG study of 30 consecutive patients with CFS	Alpha-delta sleep found in 8 patients (26%); Concluded that alpha-delta sleep is not a marker of CFS or FM. Interestingly, primary sleep disorders (sleep apnea, PLMs, narcolepsy) were present in 10 patients (33%)

Table 1 (*continued*)

Reference	Nature of study	A-D findings, comments
Branco et al., 1994 [40]	PSG study of 10 FM patients and 14 healthy controls	FM patients had increased percentage of wake and stage 2 NREM sleep with reduction of stage 4 NREM sleep and REM sleep. Alpha-delta patterns (visually and computer analyzed) occurred in 9/10 FM patients. No mention in controls. Increased alpha-delta ratio in FM patients
Kempenaers et al., 1994 [80]	A study of an antidiencephalon immune serum, amitryptiline, or placebo in 23 women with FM	'Visual inspection of sleep recording by an experienced rater (L.F.) revealed no abnormal intrusion of alpha waves in non-REM sleep'
Drewes et al., 1994 [81]	Two-night ambulatory EEG study of 12 women with FM and 14 age-matched controls. All 2-s segments of EEG were subjected to frequency analysis using autoregressive modeling. The power in the alpha band relative to the total power was calculated in all epochs	Frequency analysis demonstrated more energy in the alpha band in stages 2–4 NREM and more alpha EEG variance in FM patients. This study was performed because the authors did not find the alpha EEG difference in in-laboratory studies and postulated poor sleep in the artificial laboratory setting. No respiratory monitoring
Drewes et al., 1995 [82]	Frequency analysis of sleep in 12 women with FM and 14 controls (same patients and controls as 1994 study)	Found a predominance of the EEG power in the higher frequency bands in FM patients, and a decrease of the low-frequency parts. The increase in the alpha frequency band was not statistically significant
Drewes et al., 1995 [83]	Frequency analysis of sleep in 12 women with FM and 14 controls (same patients and controls as 1994 study). Patients with FM had more energy in the alpha-band in all NREM stages, but differences did not reach significant level, when individual sleep stages were compared	The authors had the impression of a greater variability in the alpha power in the FM patients, so further statistics were employed – constructing a common learning set for a probabilistic classifier. There was more intercycle-variance in patients with FM, but was significant only in stage 3 NREM sleep. This unprecedented and unvalidated statistical manipulation identified something statistically significant but of unknown clinical relevance. Multiple manipulations of the data revealed increased power in the alpha and sigma frequency ranges. There is no reference other than a Ph.D. thesis cited to validate this bizarre and unconventional computer manipulation of EEG data. A Medline search from 1985 to present revealed no citations
Leventhal et al., 1995 [84]	Controlled study of 8 patients with FM, 8 with generalized musculoskeletal pain without FM, and 8 normal controls. With the exception that FM patients had less stage 1 NREM sleep, there were no differences among the group in any sleep parameter	Visual scoring of alpha-NREM revealed no differences in alpha-NREM percentages among the three groups, nor did any group differ in sleep stage or in epoch-to-epoch alpha-NREM variability
Carette et al., 1995 [85]	Study of the response to treatment with amitriptyline in 22 patients with FM	The alpha NREM sleep anomaly was present in 8 (36%) at baseline; Conclusion: the alpha NREM sleep anomaly is present in only a small proportion of patients with fibromyalgia and does not correlate with disease severity nor is it affected by treatment with amitriptyline

Table 1 (*continued*)

Reference	Nature of study	A-D findings, comments
Greenberg et al., 1995 [86]	11 patients with Lyme disease and 10 controls; Subjectively, patients complained of sleep onset insomnia (27%), frequent nocturnal awakenings (27%), EDS (73%) and restless legs/nocturnal leg jerking (9%). Objectively, there was increased sleep latency, reduced sleep efficiency, and a greater arousal index. MSLTs did not reveal objective hypersomnia	Alpha intrusions into NREM sleep were present in 3/11 patients. No mention made of its presence or absence in controls
Perlis et al., 1966 [87]	20 patients with FM allowed to sleep 60 minutes to be classified as high (9) or low (11) alpha generators. The two groups were compared for performance on two memory tasks, perceptions of sleep and EEG arousals to auditory stimuli. Correlations between symptoms of FM and alpha activity were examined. Alpha activity during sleep in FM patients was associated with the perception of shallow sleep and increased tendency to arouse in relation to auditory stimuli. Alpha activity was not associated with increased memory to auditory stimuli presented during sleep, sleep state misperception, or with myalgia symptoms	'Alpha sleep appears to be, elecrophysiologically, a shallow form of sleep...and that it is perceived as such and that it is also associated with increased arousability'. No controls with which to compare 'high' and 'low' alpha generators. The 'high' alpha patient PSG example is of phasic, not tonic, alpha frequency activity. It is difficult to infer clinical relevance of alpha-EEG activity, as the 'high' and 'low' alpha generators presumably had comparably severe FM
Cote and Moldofsky, 1997 [88]	10 female patients with FM and 9 female controls; The only significant difference in objective sleep measures was more stage 1 NREM sleep in the patient group	'Alpha frequency in non-REM sleep did not differ between groups by global rating (entire night), by sleep stage (stages 2, 3, 4) or by time of night (thirds) for 10 patient records and 7 comparison group records). Changed rating scale to 0–5. Stated no difference between groups. No numerical data provided. No difference in alpha EEG between patients and controls. This was attributed to 'small sample size' and to the fact that 3/7 controls had 'high alpha' and may have had a predisposition to pain or fatigue symptoms and to the fact that 5/10 FM patients had 'atypically low alpha rating of 2″, possibly associated with improvement in the quality of sleep and severity of their symptoms during the warm summer months when the study was carried out! The 'small sample size' is larger than that in the initial 1975 report describing the 'alpha delta phenomenon'
Sharpley et al., 1997 [22]	PSG study of 20 patients with CFS and 20 controls	'Two CFS patients and none of the healthy subjects exhibited alpha wave intrusion into slow wave sleep'. What constituted 'alpha wave intrusion' was not specified. No monitoring for sleep-disordered breathing or PLMs.
Drewes et al., 1997 [89]	Measured alpha EEG during 10 seconds following painful stimulus	Not applicable to alpha EEG phenomenon. Measured transient (phasic) alpha EEG activity following painful stimulus
Drewes et al., 1998 [90]	Sleep recordings in 41 out-patients with RA and 19 matched controls. Sleep-wake interactions were evaluated using a 'graphical chain model'. There was an increase in PLMs in RA patients, but only minor differences in sleep architecture	Data from frequency analysis showed an increase in alpha EEG activity in stages 2–4 NREM sleep 'in most sleep cycles'. Only the increase in PLMs and alpha EEG activity distinguished the sleep in RA patients from that of controls. The unvalidated 'graphical chain model' used again

Table 1 (*continued*)

Reference	Nature of study	A-D findings, comments
Morehouse et al., 1998, [24]	PSG study of 42 CFS patients	'No evidence of excessive alpha EEG was seen in the group as a whole'
Scharf et al., 1998 [91]	11 FM patients studied to determine the efficacy of GHB	Baseline study: alpha intrusion % non-REM epochs (32.3) (19.83); No controls
Older et al., 1998 [32]	13 normal subjects: evaluation of effect of 3 nights of SWS interruption on pain threshold compared with 6 controls. (attempt to replicate Moldofksy's 1975 study)	No lowering of pain threshold compared to controls. (The pain threshold of normals was lower in the morning, and was accentuated by SWS fragmentation.); Failure to replicate Moldofsky's 1975 study
Lentz et al., 1999 [33]	Selective SWS deprivation using auditory stimuli in 12 normal sedentary middle-age women. Employed an automated SWS deprivation protocol that almost completely removed SWS. Outcome measures: PSG sleep, tender point plain threshold, skinfold tenderness, reactive hyperemia, somatic symptoms, and mood. Subjects showed a decrease in musculoskeletal pain threshold after the third SWSD night. Also reported increased discomfort, tiredness, fatigue, and reduced vigor. The flare response was greater after the first and third SWSD night. (The flare response was not statistically significant)	'There were no changes in the median number of epochs containing $>$ 3 s of both alpha and delta wave counts as an indicator of alpha EEG sleep'; No controls

The entire issue of subjective fatigue so far has evaded quantification. Future fatigue scales which differentiate between true excessive daytime sleepiness and fatigue must be developed.

The overwhelming conclusion is that FM and CFS are associated with sleep *complaints*, but there is no scientifically valid evidence that they represent sleep *disorders*. Furthermore, despite the tendency to attribute somatic symptoms to 'poor sleep', it must be remembered that there is no evidence that any organ of the body (including muscles and joints) other than the brain benefits from or is restored by sleep [28].

References

[1] Wolfe F, Hawley DJ, Cathey MA, Caro X, et al. Fibrositis syndrome: symptom frequency and criteria for diagnosis. J Rheumatol 1985;12:1159–1163.
[2] Thompson JM. Tension myalgia as a diagnosis at the Mayo Clinic and its relationship to fibrositis, fibromyalgia, and myofascial pain syndrom. Mayo Clin Proc 1990;65:1237–1248.
[3] Bohr TW. Fibromyalgia syndrome and myofascial pain syndrome. Do they exist? Neurol Clin 1995;13:365–384.
[4] Quintner JL, Cohen ML. Fibromyalgia falls foul of a fallacy. Lancet 1999;353:1092–1094.
[5] Cohen ML. Fibromyalgia syndrome, a problem of tautology. The Lancet 1993;342:906–909.
[6] Wolfe F. The fibromyalgia problem. J Rheumatol 1997;24:1247–1249.
[7] Hadler NM. Fibromyalgia: la maladie est morte. Vive le malade! J Rheumatol 1997;24:1250–1252.
[8] Bohr T. Problems with myofascial pain syndrome and fibromyalgia syndrome. Neurology 1996;46:593–597.
[9] Wolfe F, Cathey MA. The epidemiology of tender points: a prospective study of 1520 patients. J Rheumatol 1985;12:1164–1168.
[10] Smythe H. Tender points: evolution of concepts of fibrositis/fibromyalgia syndrome. Am J Med 1986;81(Suppl 3A):2–6.
[11] Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis Rheumatism 1986;29:1371–1377.
[12] White KP, Speechley M, Harth M, Ostbye T. The London fibromyalgia epidemiology study: comparing teh demographic and clinical characteristics in 100 random community cases of fibromyalgia versus controls. J Rheumatol 1999;26:1577–1585.
[13] Bennett RM. Beyond fibromyalgia: ideas on etiology and treatment. J Rheumatol 1989;16(Suppl 19):185–191.
[14] Horne JA, Moore VJ. Sleep EEG effects of exercise with and without additional body cooling. EEG Clin Neurophysiol 1985;60:33–38.
[15] Horne JA, Reid AJ. Night-time sleep EEG changes following body heating in a warm bath. EEG Clin Neurophysiol 1985;60:154–157.

[16] Moldofsky H, Saskin P, Lue FA. Sleep and symptoms of fibrositis syndrome following a febrile illness. J Rheumatol 1988;15:1701–1704.
[17] Whelton C, Saskin P, Salit I, Moldofsky H. Sleep and symptoms in post-viral fatigue syndrome. Soc Biol Psychiatry 1988 (presentation).
[18] Gupta MA, Moldofsky H. Dysthymic disorder and rheumatic pain modulation disorder (fibrositis syndrome): a comparison of symptoms and sleep physiology. Can J Psychiatry 1986;31:608–616.
[19] Goldenberg DL. Fibromyalgia and its relation to chronic fatigue syndrome, viral illness, and immune abnormalities. J Rheumatol 1989;16(Suppl 19):91–93.
[20] Komaroff AL, Goldenberg D. The chronic fatigue syndrome: definition, current studies and lessons for fibromyalgia research. J Rheumatol 1989;16(Suppl 19):23–27.
[21] Fukuda K, Straus SE, Hickie I, Sharpe MC, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121:953–959.
[22] Sharpley A, Clements A, Hawton K, Sharpe M. Do patients with "pure" chronic fatigue syndrome (neurasthenia) have abnormal sleep? Psychosom Med 1997;59:592–596.
[23] Stores B, Fry A, Crawford C. Sleep abnormalities demonstrated by home polysomnography in teenagers with chronic fatigue syndrome. J Psychosom Res 1998;45:85–91.
[24] Morehouse RL, Flanigan M, MacDonald DD, Braha D, et al. Depression and short REM latency in subjects with chronic fatigue syndrome. Psychosom Med 1998;60:347–351.
[25] Mahowald MW, Nicol S, Culliton P, Brummitt C, et al. Chronic Epstein–Barr virus (CEBV) syndrome: objective measurements of nighttime sleep and daytime sleepiness. Sleep Res 1988;17:292.
[26] Flanigan MJ, Morehouse RL, Shapiro CM. Determination of observer-rated alpha activity during sleep. Sleep 1995;18:702–706.
[27] Krupp LB, Jandorf L, Coyle PK, Mendelson WB. Sleep disturbance in chronic fatigue syndrome. J Psychosom Res 1993;37:325–331.
[28] Horne JA. Tissue restitution and sleep, with particular reference to human slow wave sleep. In: Borbely AA, Inoue S, editors. Endogenous sleep substances and sleep regulation, Tokyo, Japan: Scientific Societies Press, 1985. pp. 25–40.
[29] Hauri P, Hawkins DR. Alpha-delta sleep. EEG Clin Neurophysiol 1973;34:233–237.
[30] Moldofsky H, Scarisbrick P, England R, Smythe H. Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. Psychosom Med 1975;37:341–351.
[31] Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep state deprivation. Psychosom Med 1976;38:35–44.
[32] Older SA, Battafarano DF, Danning CL, Ward JA, et al. The effects of delta wave sleep interruption on pain thresholds and fibromyalgia-like symptoms in healthy subjects: correlations with insulin-like growth factor I. J Rheumatol 1998;25:1180–1186.
[33] Lentz MJ, Landis CA, Rothermel J, Shaver JLF. Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. J Rheumatol 1999;26:1586–1592.
[34] Fry JM, Pressman MR, DiPhillipo MA. Alpha-delta sleep and disorders of excessive somnolence. Sleep Res 1987;16:333.
[35] Scheuler W, Kubicki S, Marquardt J, Scholz G. The alpha-sleep pattern: quantitative analysis and functional aspects, 1988. pp. 284–286.
[36] Scheuler W, Rappelsbeger R, Schmatz F. Periodicities of the alpha-sleep pattern. Sleep Res 1987;16:638.
[37] Scheuler W, Kubicki S. Characteristics of the alpha sleep pattern. EEG Clin Neurophysiol 1986;64:13.
[38] Scheuler W, Haag C, Kubicki S. Phasic events during sleep in subjects with alpha-sleep pattern. Sleep Res 1987;16:425.
[39] Moldofsky H, Lue FA, Saskin P. Sleep and morning pain in primary osteoarthritis. J Rheumatol 1987;14:124–128.
[40] Branco J, Atalaia A, Paiva T. Sleep cycles and alpha-delta sleep in fibromyaglia syndrome. J Rheumatol 1994;21:1113–1117.
[41] Horne J, Shackell BS. Alpha-like EEG activity in non-REM sleep and the fibromyalgia syndrome. EEG Clin Neurophysiol 1991;79:271–276.
[42] Moldofsy H, Scarisbrick P, England R, Smythe H. Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. Psychosom Med 1975;37:341–351.
[43] MacFarlane JG, Shahal B, Mously C, Moldofsky H. Periodic K-alpha sleep EEG activity and periodic limb movements during sleep: comparison of clinical features and sleep parameters. Sleep 1996;19:200–204.
[44] Terzano MG, Parrino L. Functional relationship between micro- and macrostructure of sleep. In: Terzano MG, Halasz PL, Declerk AC, editors. Phasic events and dynamic organization of sleep, New York: Raven Press, 1991. pp. 101–119.
[45] Terzano MG, Mancia D, Salati MR, Costani G, et al. The cyclic alternating pattern as a physiologic component of NREM sleep. Sleep 1985;8:137–145.
[46] Terzano MG, Parrino L, Spaggiari MC. The cyclic alternating pattern sequences in the dynamic organization of sleep. EEG Clin Neurophysiol 1988;69:437–447.
[47] Scheuler W, Rappelsberger P, Schmatz F, Pastelak-Price C, et al. Periodicity analysis of sleep EEG in second and minute ranges – example of application in different alpha activities in sleep. EEG Clin Neurophysiol 1990;76:222–234.
[48] May KP, West SG, Baker MR, Everett DW. Sleep apnea in male patients with the fibromyalgia syndrome. Am J Med 1993;94:505–508.
[49] Donald F, Esdaile JM, Kimoff JR, Fitzcharles M-A. Musculoskeletal complaints and fibromyalgia in patients attending a respiratory disease clinic. J Rheumatol 1996;23:1612–1616.
[50] Molony RR, MacPeek DM, Schiffman PL, Frank M, et al. Sleep, sleep apnea, and the fibromyalgia syndrome. J Rheumatol 1986;13:797–800.
[51] Saskin P, Moldofsky H, Lue FA. Sleep and posttraumatic rheumatic pain modulation syndrome (fibrositis syndrome). Psychosom Med 1986;48:319–323.
[52] Moldofsky H, Lue FA, Saskin P, Salem L, et al. Sleep and

symptoms in psychophysiologic persistent insomnia versus rheumatic pain modulation disorder (fibrositis syndrome). Sleep Res 1986;15:199.
[53] Moldofsky H, Saskin P, Salem L, Lue F. Sleep and symptoms in post-infectious neuromyasthenia and fibrositis syndrome. Sleep Res 1987;16:492.
[54] Engle-Friedman M, Liebermann M, Bansal S, Wincze J, et al. Sleep evaluation of alcoholics at three intervals of sobriety. Sleep Res 1987;16:475.
[55] Scheuler W, Stinsshoff D, Kubicki S. The alpha-sleep pattern. Differentiation from other sleep patterns and effect of hypnotics. Neuropsychobiology 1983;10:183–189.
[56] Ware JC, Russell IJ, Campos E. Alpha intrusions into the sleep of depressed and fibromyalgia syndrome (fibrositis) patients. Sleep Res 1986;15:210.
[57] Moldofsky H, Lue FA, Smythe H. Alpha EEG sleep and morning symptoms in rheumatoid arthritis. J Rheumatol 1983;10:373–379.
[58] Sewitch D, Kupfer DJ, Reynolds CFI. Alpha-NREM sleep distributed across the day in a legally blind elderly male. Biol Psychiatry 1986;21:201–207.
[59] Moldofsky H. Sleep and fibrositis syndrome. Rheumatic Clin N Am 1989;15:91–103.
[60] Kumar A, Schneider-Helmert D. Quantitative verification of alpha sleep. Sleep Res 1997;26:227.
[61] Pivik RT, Harman K. A reconceptualization of EEG alpha activity as an index of arousal during sleep: all alpha activity is not equal. J Sleep Res 1995;4:131–137.
[62] Solomon DH, Liang MH. Fibromyalgia: scourge of humankind or bane of a rheumatologist's existence. Arthritis Rheumatism 1997;40:1553–1555.
[63] Gordon DA. Fibromyalgia – out of control?. J Rheumatol 1997;24:1247.
[64] Van Sweden B. Alpha-delta sleep or the continuing alpha-story. Acta Neurol Belg 1995;95:5–7.
[65] Moldofsky H, Lue FA. The relationship of alpha and delta EEG frequencies to pain and mood in 'fibrositis' patients treated wtih chlorprmazine and l-tryptophan. EEG Clin Neurophysiol 1980;50:71–80.
[66] Moldofsky H, Tullis C, Lue FA, Quance G, et al. Sleep-related myoclonus in rheumatic pain modulation of disorder (fibrositis syndrome) and in excessive daytime somnolence. Psychosom Med 1984;46:145–151.
[67] Moldofsky H, Tullis C, Lue FA. Sleep related myoclonus in rheumatic pain modulation disorder (fibrositis syndrome). J Rheumatol 1986;13:612–617.
[68] Saskin P, Moldofsky H, Lue FA. Periodic movements in sleep and sleep-wake complaint. Sleep 1985;8:319–324.
[69] Touchon J, Besset A, Billiard M, Simon L, Herrisson C, Cadilhac J. Fibrositis syndrome: polysomnographic and psychological aspects. In: Koella WP, Obal F, Schulz H, Visser P, editors. Sleep '86, Stuttgart: Gustav Fischer Verlag, 1988. pp. 445–447.
[70] Crosby LJ. EEG sleep variables of rheumatoid arthritis patients. Arthritis Care Res 1989;1:198–204.
[71] Silva AB, Bertorini TE, Lemmi H. Polysomnography in idiopathic muscle pain syndrome (fibrositis). Arquivos De Neuro Psiquiatria 1991;49:437–441.
[72] Anch AM, Lue FA, MacLean AW, Moldofsky H. Sleep physiology and psychological aspects of the fibrositis (fibromyalgia) syndrome. Can J Psychol 1991;45:179–184.
[73] Reynolds WJ, Moldofsky H, Saskin P, Lue FA. The effects of cyclobenzaprine on sleep physiology and symptoms in patients with fibromyalgia. J Rheumatol 1991;18:452–454.
[74] Whelton CL, Salit I, Moldofsky H. Sleep, Epstein–Barr virus infection, musculoskeletal pain, and depressive symptoms in chronic fatigue syndrome. J Rheumatol 1992;19:939–943.
[75] Morriss R, Sharpe M, Sharpley AL, Cowen PJ, et al. Abnormalities of sleep in patients with the chronic fatigue syndrome. Br Med J 1993;306:1161–1164.
[76] Moldofsky H, Wong MTH, Lue FA. Litigation, sleep, symptoms and disabilities in postaccident pain (fibromyalgia). J Rheumatol 1993;20:1935–1940.
[77] Doherty M, Smith J. Elusive 'alpha-delta' sleep in fibromyalgia and osteoarthritis. Ann Rheumatic Dis 1993;52:245.
[78] Hirsch M, Carlander B, Verge M, Tafte M, et al. Objective and subjective sleep disturbances in patients with rheumatoid arthritis. A reappraisal. Arthritis Rheumatism 1994;37:41–49.
[79] Manu P, Lane TJ, Matthews DA, Castriotta RJ, et al. Alpha-delta sleep in patients with a chief complaint of chronic fatigue. Southern Med J 1994;87:1289–1290.
[80] Kempenaers C, Simenon G, Vander Elst M, Fransolet L, et al. Effect of an antidiencephalon immune serum on pain and sleep in primary fibromyalgia. Neuropsychobiology 1994;30:66–72.
[81] Drewes AM, Svendsen L, Nielsen KD, Taagholt SJ, et al. Quantification of alpha-EEG activity in fibromyalgia: a study based on ambulatory sleep monitoring. J Musculoskel Pain 1994;2:33–53.
[82] Drewes AM, Nielsen KD, Taagholt SJ, Bjerregard K, et al. Sleep intensity in fibromyalgia: focus on the microstructure of the sleep process. Br J Rheumatol 1995;34:629–635.
[83] Drewes AM, Gade J, Nielsen KD, Bjerregard K, et al. Clustering of sleep electroencephalographic patterns in the fibromyalgia syndrome. Br J Rheumatol 1995;34:1151–1156.
[84] Leventhal L, Freundlich B, Lewis J, Gillen K, et al. Controlled study of sleep parameters in patients with fibromyalgia. J Clin Rheumatol 1995;1:110–113.
[85] Carette S, Oakson G, Guimont C, Steriade M. Sleep electroencephalography and the clinical response to amitriptyline in patients with fibromyalgia. Arthritis Rheumatism 1995;38:1211–1217.
[86] Greenberg HE, Ney G, Scharf SM, Ravdin L, et al. Sleep quality in Lyme disease. Sleep 1995;18:912–916.
[87] Perlis ML, Giles DE, Bootzin RR, Dikman ZV, et al. Alpha sleep and information processin, perception of sleep, pain, and arousability in fibromyalgia. Int J Neurosc 1996;89:265–280.
[88] Cote KA, Moldofsky H. Sleep, daytime symptoms, and cognitive performance in patients with fibromyalgia. J Rheumatol 1997;24:2014–2023.

[89] Drewes AM, Nielsen KD, Arendt-Nielsen L, Birket-Smith L, et al. The effect of cutaneous and deep pain on the electroencephalogram during sleep – an experimental study. Sleep 1997;20:632–640.

[90] Drewes AM, Svendsen L, Taagholt S, Bjerregard K, et al. Sleep in rheumatoid arthritis: a comparison with healthy subjects and studies of sleep/wake interactions. Br J Rheumatol 1998;37:71–81.

[91] Scharf MB, Hauck M, Stover R, McDannold M, et al. Effect of gamma-hydroxybutyrate on pain, fatigue, and the alpha sleep anomaly in patients with fibromyalgia. Preliminary report. J Rheumatol 1998;25:1986–1990.