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13. ABSTRACT (Maximum 200 words)

Fibromyalgia (FMS) is a chronic musculoskeletal pain syndrome of unknown etiology. Proposed hypotheses include delta wave sleep disturbances, aerobic deconditioning, and low serum levels of insulin-like growth factor-1 (IGF-1). We subjected 19 healthy volunteers to 2 levels of delta wave sleep interruption (DWSI) and compared the effects on pain sensitivity (PS) and symptoms to 6 controls. PS and symptoms increased incrementally between controls (Grp1), subjects undergoing stage 4 DWSI (Grp2, n=6), and those undergoing stage 3 and 4 DWSI (Grp3; n=13). Three of 6 Grp2 ($p=0.18$) and 8/13 Grp3 ($p=0.020$) developed increased PS following 3 days of DWSI. All Grp3 subjects demonstrated increased overnight PS; this was observed in Grp1 to a lesser degree ($p=0.22$). Grp3 subjects developed significant fatigue ($p=0.001$) and neck/shoulder pain ($p=0.02$) compared with Grp1 subjects. No correlations were observed between PS and levels of physical fitness ($r=-0.18$, $p=0.463$). No significant changes in serum levels of IGF-1 occurred following DWSI ($p=0.298$). Delta wave sleep interruption produces dose dependent increases in PS and symptoms. Increased morning PS is common in normal individuals, and is worsened by DWSI. Aerobic conditioning was not protective against the development of DWSI-induced PS or symptoms.

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic and debilitating illness characterized by diffuse musculoskeletal pain, nonrestorative sleep, and the presence of localized tenderness at characteristic sites (1-4). An estimated three to six million Americans are affected (5). The prevalence of FMS in the general population has recently been assessed at roughly 2.0% (6). It occurs most commonly in females between the ages of 20 and 60 years, but all ages and both genders are susceptible (2). The incidence and sex ratio of FMS in the active duty military population is unknown, however it may be responsible for many of the musculoskeletal complaints evaluated at troop medical clinics and military hospitals. At the Brooke Army Medical Center Rheumatology Clinic, 35 of 83 (43%) FMS patients fall within the typical active duty age range (less than 50 years of age), and 20% are less than 40 years of age. During Operation Desert Storm soft tissue rheumatic disease accounted for 22% of outpatient visits over a one month period (7). Several soldiers required air evacuation to CONUS because of FMS (personal communication, Gary L. Klipple, COL, MC); at least two were medically retired.

The etiology and pathogenesis of FMS are unclear. Research into potential causes has included three major areas of interest: disturbances of sleep, physical deconditioning, and abnormalities of the neuroendocrine system. The influence of sleep disturbances on pain modulation is poorly understood. In humans sleep is characterized by alternating cycles of rapid eye movement (REM) and non-REM sleep. The later is subdivided into four stages based on the relative presence of low frequency brain waves called delta waves. Stages 3 and 4, where delta wave density is highest, have traditionally been referred to as deep or slow wave sleep. It is in slow wave sleep that restorative processes are thought to take place (8-9) and it is here that certain neurohormonal substances such as seratonin, gamma-aminobutyric acid (GABA), prolactin, and the growth hormone-IGF-1 system are thought to be active (10). Abnormalities of slow wave sleep have been associated with a number of somatic symptoms (11). In 1975, Moldofsky et al demonstrated significant alpha wave intrusion during delta wave sleep in seven of ten FMS patients (12). The remaining three patients had little or no baseline delta wave sleep. This disturbance of non-REM deep sleep, referred to as the

alpha-delta anomaly, was then experimentally induced by arousing normal subjects as they entered stage 4 sleep. Within three days of selective stage 4 delta wave sleep interruption (DWSI), all subjects complained of musculoskeletal aching and stiffness and had increased pain sensitivity (PS) by dolorimetry testing that resolved upon restoration of normal sleep (12). Similar changes could not be induced by selective REM sleep interruption (13).

During these studies Moldofsky noted that DWSI-induced symptoms did not appear in three well-conditioned long distance runners (13). He suggested that aerobic conditioning may be protective against "fibrositic" symptoms. In 1988 McCain et al showed that improvement in aerobic conditioning can improve symptoms in FMS patients (14). Bennett later found that aerobic conditioning was below average in greater than 80 percent of 25 female patients with FMS (15). These data collectively suggest that aerobic conditioning may prevent increases in pain sensitivity in persons subjected to disturbed delta wave sleep.

Serum levels of insulin-like growth factor-1 (IGF-1) are low in FMS (10,16). This hormone is produced by the liver under the influence of growth hormone and may play a reparative role in tissue microtrauma (17). Since growth hormone is released during delta wave sleep, it has been hypothesized that delta wave sleep disruption may result in low levels of IGF-1, incomplete repair of muscle microtrauma and subsequent chronic myalgia (17).

The goals of the present study were to determine: 1) if the induction of the alpha-delta sleep anomaly by selective DWSI causes fibromyalgia symptoms, 2) if prior aerobic conditioning reduces the incidence of fibromyalgia symptoms in sleep-interrupted individuals, and 3) if serum levels of IGF-1 decrease as a result of DWSI.

METHODS

STUDY POPULATION:

Twenty-five healthy college student and active duty military volunteers between the ages of 18-40 years were studied. Volunteers with known psychiatric or musculoskeletal disorders, documented/probable nocturnal myoclonus or sleep apnea,
any chronic medical condition requiring regular monitoring or medication, or a history of drug and/or alcohol abuse were excluded. Detection during initial evaluation of any significant untreated medical condition, pregnancy, or an abnormal baseline EEG also resulted in exclusion from the study. Subjects were instructed to abstain from the use of any drugs or alcohol during the study and to avoid coffee or tea after 1000 hours. They were encouraged to maintain their daily routine and to refrain from daytime sleep.

The study population comprised three groups: an initial group of six college student volunteers underwent selective stage 4 DWSI (Grp2); subsequent subjects comprising a mixture of college student and military volunteers were randomly assigned to undergo stage 3 and 4 DWSI (Grp3; n=13) or serve as controls
(Grp1; n=6).

SLEEP STAGE INTERRUPTION:

Grp2 and Grp3 subjects were monitored for five consecutive nights in a sleep laboratory. One night of undisturbed sleep (baseline) was followed by three nights of DWSI and a final night of undisturbed sleep (recovery). Sleep data was collected on a Sleeptrace 2000 Digital Polysomnograph: two electroencephalo-gram, 2 electrooculogram, 1 chin electromyogram, and 1 precordial electrocardiogram channels were monitored on a 17 inch color monitor at 10 mm/sec scroll speed by an experienced technologist. Data was archived onto magnetic data cassettes for off-line scoring by a board certified sleep specialist (SD). During nights 2, 3, and 4 subjects were aroused from delta wave sleep by an auditory stimulus delivered through an earplug, or by physical stimulation (shaking) as required. Sleep was scored manually in 30 second epochs, according to Rechtschaffen and Kales criteria (18). Delta wave sleep was identified as electroencephalographic waves with amplitude equal to or greater than 75 microvolts, and frequencies of 0.5

to 2 cycles per second. Stage 3 sleep was defined as 20-50% delta waves in a 30 second epoch; stage 4 was defined as 51-100% delta waves in a 30 second epoch. Arousal was defined as a change to stages 0, 1, or 2 for at least 20 seconds but less than 60 seconds. "Awake" was defined as stage 0 for 60 seconds or more.

DOLORIMETRY AND SYMPTOM ASSESSMENT:

Dolorimetry and symptom assessment were performed each morning and evening within 1 hour of sleep. Dolorimetry was performed by one of two blinded rheumatologists using a 20 kilogram pressure dolorimeter on a 1.54 square centimeter stopper applied to each of the 18 characteristic tender point sites defined by the American College of Rheumatology 1990 Criteria for Fibromyalgia (19). Increasing pressure was applied at approximately 1 kilogram per second to the point of "pain," indicated by either verbal response or withdrawal. The kilograms of pressure tolerated at each site were recorded to the nearest one-tenth kilogram. Values from all eighteen sites were averaged to give a mean dolorimetry score. The mean score obtained at the first measurement became the baseline score for each subject. Subsequent mean dolorimetry scores were divided by the baseline score to give a normalized score. Normalized scores for each subject were then averaged together within groups to yield a composite normalized group score. Changes in sensitivity to pain were assessed by measurement of dolorimetry score ratios (DSR). For the purposes of this study, "overnight DSR" was defined as the ratio of the morning dolorimetry score divided by the evening dolorimetry score. "Across study DSR" was defined as the ratio of dolorimetry score from the morning following the final night of sleep interruption (Friday morning) divided by that of the baseline morning (Tuesday morning). Dolorimetry score ratios less than one reflected an increased sensitivity to pain.

Two rheumatologists (SAO, DFB) were trained by an expert (IJR) in dolorimetry testing and practiced in comparative fashion before the start of the study. Inter-observer reliability of dolorimetry was determined by a linear regression analysis of blinded measurements at 36 tender points on two separate control subjects.

Seventeen musculoskeletal, neuropsychiatric, and gastrointestinal symptoms were self-assessed using visual

analog scales. Composite symptoms during DWSI were measured as maximum percent increase from baseline.

BICYCLE ERGOMETRY:

Within three weeks following DWSI and after a four hour fast, each study subject was exercised on a Bosch ERG500 electromechanically braked bicycle ergometer using an incremental protocol. Following 1 minute of unloaded pedaling, the workload was increased by 25 watts per minute until volitional exhaustion. The level of physical conditioning was reported as maximum workload measured in watts/kg and compared with normal age-matched controls (20).

INSULIN-LIKE GROWTH FACTOR-1 (IGF-1):

Blood was drawn from all sleep-interrupted subjects between 0600-0700 hours on the mornings following the first (baseline), fourth (post-DWSI), and fifth (recovery) nights. Serum was stored at minus 70 degrees centigrade and later analyzed for levels of IGF-1 using a competitive binding radioimmunoassay as previously described (16).

CONTROL SUBJECTS:

Control subjects were used as a comparison group for dolorimetry scores. They were asked to abide by the same daytime restrictions as the sleep-interrupted subjects, but slept uninterrupted at home and did not participate in blood collection or bicycle ergometry. In the laboratory, they underwent dolorimetry testing and visual analog assessments by a rheumatologist blinded to their sleep history.

STATISTICAL ANALYSIS:

Dolorimetry and sleep study data were analyzed using a two way (group, time) repeated measures analysis of variance with repeated measures on one factor (time). Visual analog scaled symptoms were analyzed using a two-tailed student t test.

RESULTS

STUDY POPULATION:

The study groups consisted of male and female college students and soldiers ranging in age from 18 to 40 years. Average ages were 24 years for Grp1, 20 years for Grp2, and 23 years for Grp3. Two of 6 Grp1 (17%), 3 of 13 Grp2 (33%) and 1 of 6 Grp3 (23%) were female. All Grp2 subjects were college students, while 4/6 Grp1 and 8/13 Grp3 were soldiers (Table 1).

SLEEP DATA:

Analysis of sleep in Grp2 and Grp3 subjects included measurements of total sleep time, sleep latency, REM latency, number of arousals, and sleep stage percentages (Tables 2 and 3). There were no significant differences between or within groups for total sleep time, sleep or REM latency, number of arousals, or percentage of REM sleep. Sleep interruption in both groups resulted in a decrease in percent of stage 4 sleep and a relative increase in early sleep stages, principally stage 2. Stage 4 sleep deprivation was more complete in Grp3, and was similar to that obtained in the Moldofsky study (12) during the first night of DWSI (Table 4 and Figure 1).

DOLORIMETRY AND SYMPTOM ASSESSMENT:

No significant differences between conditions (baseline, DWSI, recovery) could be detected within any of the 3 groups. In comparisons between groups, variation in mean dolorimetry scores in Grp2 was minimal (Figure 2). Average overnight DSR during the three nights of DWSI reflected a significant increase in overnight pain sensitivity in Grp1 and Grp3 ($p=0.001$). Significant differences between groups was also detected ($p=<0.05$) (Table 5). Average across study DSR revealed increased sensitivity to pain in Grp3 only ($p=0.10$) (Table 5). None of the Grp1 subjects developed an across study DSR of less than one, compared with 3/6 Grp2 subjects ($p=0.18$) and 8/13 Grp3 subjects ($p=0.02$, Fisher's exact test).

Assessment of inter-observer variability of dolorimetry testing demonstrated high correlation by linear regression analysis ($r=0.94$; SE Yest=1.7).

Grp1 subjects demonstrated no significant symptoms during the study. Grp2 subjects developed statistically significant fatigue ($p=0.022$) compared with controls. Grp3 subjects

developed significant fatigue (p=0.001) and neck/shoulder pain (p=0.014). Other symptoms were prominent, but did not reach statistical significance (Figure 3). One of 6 Grp1, 2/6 Grp2 (p=1.00), and 7/13 Grp3 (p=0.18) subjects developed an increase in more than one symptom during DWSI (Fisher's exact test).

BICYCLE ERGOMETRY:

Eleven of 19 subjects exercised to within 90-110 percent of normal based on age-matched normal controls (20). Three subjects were considered "exceptionally fit" and 5 were classified as "sedentary." No correlation between aerobic conditioning and across study DSR was found (r=-0.18, p=0.463). Two of 5 "sedentary" subjects and 2/3 "exceptionally fit" subjects demonstrated across study DSR of less than one. Five of 6 subjects developing the lowest across study DSR were in the normal range of fitness (Figure 4).

IGF-1:

There were no significant changes noted in the levels of serum IGF-1 following DWSI (p=0.298). No correlation could be detected between baseline serum IGF-1 and level of conditioning (r=-0.29, p=0.23) or across study DSR (r=0.43, p=0.23).

DISCUSSION

The design of the present study was modeled after the Moldofsky protocol. The first 6 subjects studied were college students subjected to stage 4 DWSI (Grp2). Dolorimetry results from this group did not parallel those of the other two groups. These subjects did not demonstrate increased pain sensitivity between conditions (baseline, DWSI, recovery) as Moldofsky had shown, nor did they show an increase in pain sensitivity following DWSI (across study DSR). Overnight DSR reflected minimal change. The reasons for this absence of response are unclear. In our study sleep interruption procedures were virtually identical and yielded results no different than those of the Moldofsky protocol with two exceptions. Subjects in the Moldofsky study served as their own controls during two nights each of baseline and recovery sleep. Electroencephalographic data from Moldofsky's study revealed no significant differences between the 2 baseline nights or the 2 recovery nights (data not shown), however there may have been differences in dolorimetry scores (data not published) that allowed detection of significant differences between conditions. We used a separate control group and limited the baseline and recovery to only one night each. Failure of our subjects to fully accomodate to the laboratory environment may have masked detection of differences in DSR between conditons. Secondly, in the Moldofsky study, statistically significant increases in pain sensitivity were attributed to the first night of DWSI in which stage 4 deprivation was nearly complete. The level of DWSI delivered in the remaining 2 nights was similar to that seen in our Grp2. Stage 3 and 4 DWSI during our study resulted in stage 4 deprivation equivalent to that of Moldofsky's first night (Figure 1, Table 4). Therefore we believe data derived from Grp3 best compares to the original study.

In agreement with the Moldofsky data we too noted an increase in pain sensitivity as a result of DWSI. In Grp3, increased morning pain was statistically significant compared with controls (Figure 2, Table 5). Increased pain sensitivity following DWSI occurred in sixty-two percent of Grp3 subjects experienced compared with 50 percent in Grp2 and none in Grp1. Symptom development during DWSI followed a moderate dose-response relationship (Figure 4). In contrast with the

Moldofsky study, we failed to detect universal changes in symptoms and dolorimetry. Stage 4 DWSI resulted in minimal changes in dolorimetry by overnight or across study DSRs. By group average no statistically significant increases in pain sensitivity could be found, even with aggressive DWSI (Grp3). Only one third of Grp2 and about half of Grp3 subjects developed new or increased symptoms.

By using a control group we were able to discover that PS is increased in the mornings in normal individuals, and is worsened by DWSI. To our knowledge this has not been reported.

Regarding aerobic conditioning, no association was observed between level of conditioning and DWSI-induced symptoms and PS (Figure 3). Assessment of aerobic conditioning was performed retrospectively. A prospective study designed to enroll subjects by fitness category may allow more appropriate comparisons.

Acute DWSI caused no significant change in the serum levels of IGF-1. The suppositions that levels of this reparative hormone are directly correlated to delta wave sleep, and that low levels are associated with FMS symptoms, must be questioned. Sleep interruption in our study was acute, selective, and limited; analysis of chronic sleep disturbances may yield different results. Serum sampling frequency in this study may have missed demonstrable decrements in IGF-1. Perhaps growth hormone and IGF-1 may be influenced by factors other than DWSI. There may exist secondary physiologic pathways that are unaffected by DWSI. Baseline levels of IGF-1 showed no significant correlations to either physical conditioning or PS.

CONCLUSIONS

Development of symptoms and increased PS following selective DWSI occurs in a dose-dependent fashion, but is not invariable. Less than 2/3 of subjects undergoing aggressive DWSI develop symptoms or increased PS. The greater the degree of DWSI, the more likely the development of symptoms and increased PS. In normal individuals tolerance to pain appears to be lower in the mornings and may be worsened by DWSI.

We observed nothing to suggest aerobic fitness protects against DWSI-induced symptoms and increased PS. There is no direct evidence suggesting aerobic deconditioning is a predisposing factor. The assumption that "athletic" soldiers are more tolerant of sleep deprivation is not supported by these data, however the study design in this regard was retrospective. Randomization of sufficient numbers of subjects into fitness categories prior to sleep deprivation may yield more conclusive data.

Much more research into the role of neurotransmitters in the pathogenesis of FMS is needed. It is likely that neurotransmitters play a central role in both sleep modulation and pain thresholds. Our study design may have precluded an accurate appraisal of the relationship between IGF-1 and acute DWSI. Degree and duration of interruption and timing of blood sampling should be considered. Numerous other neurotransmitter and neurohormonal systems (serotonin, prolactin, substance P, etc) have been implicated in chronic pain syndromes and should be studied.

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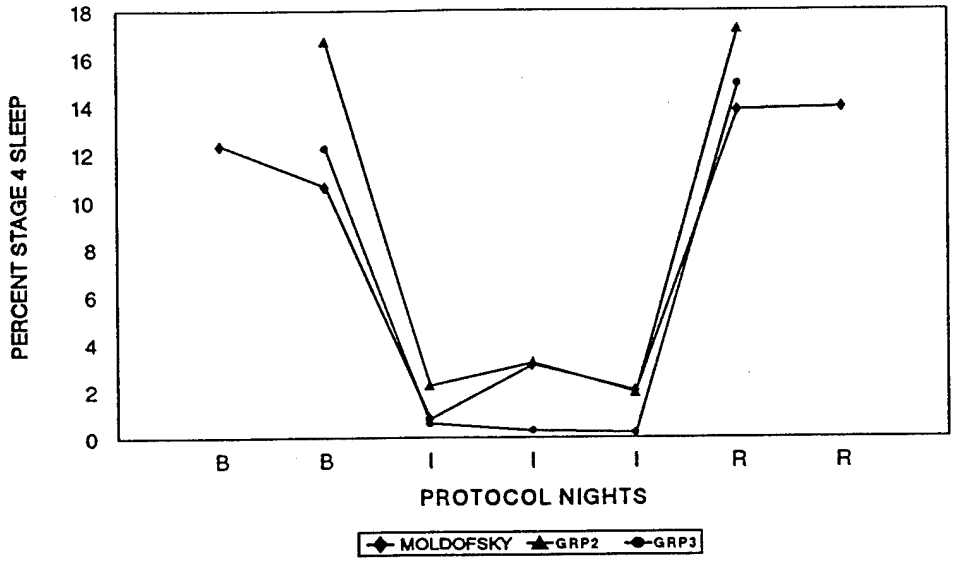

FIGURE 1: Percent stage 4 sleep during baseline (B), delta wave sleep interruption (I), and recovery (R) nights.

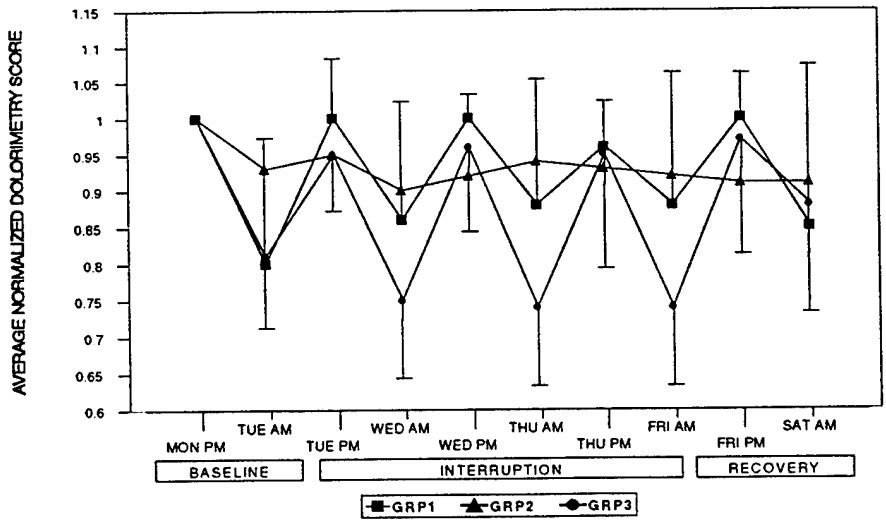

FIGURE 2: Average normalized dolorimetry scores by groups.

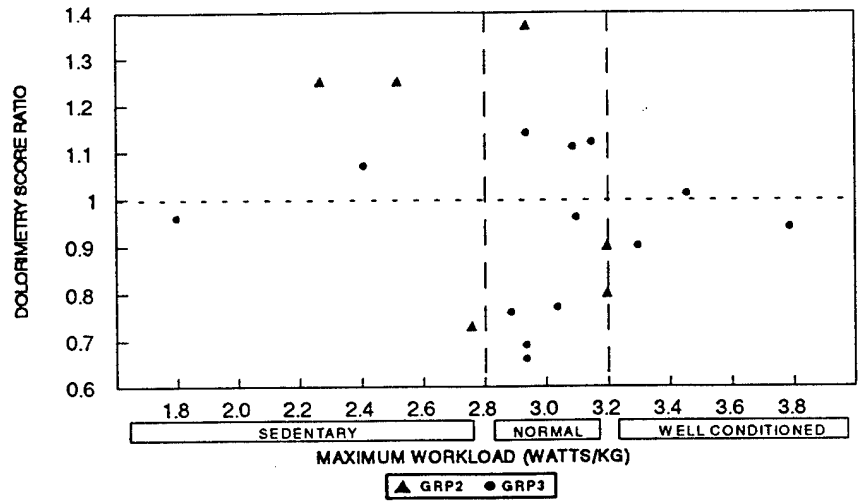

FIGURE 3: Across study DSR compared to level of aerobic conditioning as measured by maximum workload generated during bicycle ergometry. Values less than one indicate increased pain sensitivity (see text).

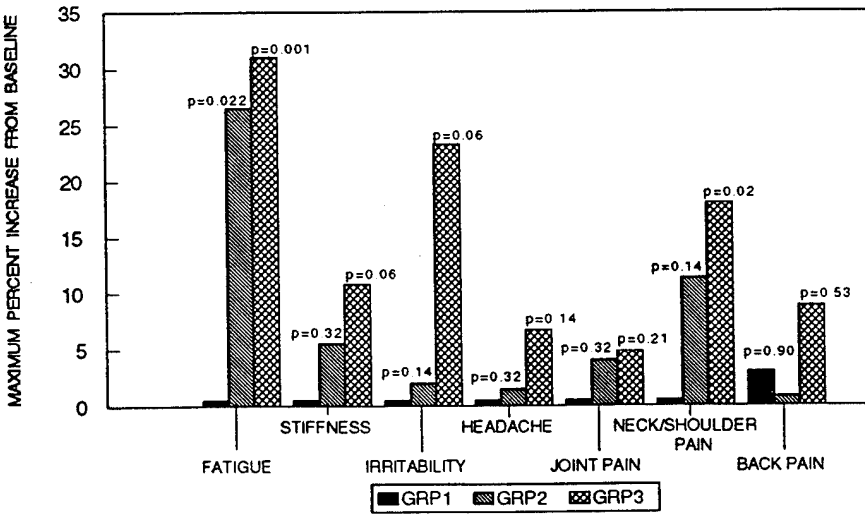

FIGURE 4: Development of symptoms during DWSI. Symptom scores were obtained by visual analog scales and reported as maximum percent increase from baseline symptoms. P values are derived from comparisons to GRP1.

TABLE 1: Demographic data of study population.

GROUP	MEAN AGE	MALE / FEMALE	COLLEGE / MILITARY	MAX WORKLOAD WATTS / KG
GRP1 (n=6)	24	5 / 1	2 / 4	----
GRP2 (n=6)	26	4 / 2	6 / 0	2.44
GRP3 (n=13)	23	10 / 3	5 / 8	2.99

TABLE 2: EEG Sleep Data: GRP2

Sleep Variable	Statistic	1 *	2	3	4	5
Total Sleep Time (min)	Mean S.D.	420.9 16.9	406.3 29.9	435.6 22.2	419.2 20.7	455.0 10.2
Sleep Latency (min)	Mean S.D.	14.2 7.2	13.8 11.7	9.7 4.8	6.0 3.0	5.3 3.4
REM Latency (min)	Mean S.D.	96.1 41.4	141.8 63.1	106.2 24.9	109.3 42.2	108.3 39.6
Number of Arousals	Mean S.D.	26.3 6.9	38.2 18.2	33.2 16.2	47.3 18.5	20.3 7.4
% Stage W †	Mean S.D.	12.9 3.6	18.1 8.9	10.3 6.0	14.8 5.6	5.2 2.3
% Stage 1	Mean S.D.	7.8 3.1	10.5 4.3	6.1 1.4	6.6 1.5	4.5 2.1
% Stage 2	Mean S.D.	50.4 4.3	58.7 10.6	57.7 7.9	57.6 8.1	52.7 7.4
% Stage 3	Mean S.D.	6.7 1.7	11.6 4.3	12.2 4.2	12.0 7.9	6.4 4.1
% Stage 4	Mean S.D.	16.7 8.2	2.2 1.6	3.2 1.8	1.9 1.4	17.2 8.0
% Stage REM	Mean S.D.	18.4 5.5	17.1 6.8	20.9 3.9	22.0 3.6	19.1 1.5

* 1 = baseline night; 2 , 3 , 4 = delta wave sleep interuption; 5 = recovery night

† W = wake

TABLE 3: EEG Sleep Data: GRP3

Sleep Variable	Statistic	1 *	2	3	4	5
Total Sleep Time (min)	Mean S.D.	390.8 72.9	398.0 52.1	409.9 37.6	411.8 24.2	432.8 38.2
Sleep Latency (min)	Mean S.D.	20.2 31.4	6.9 4.7	7.5 6.8	8.5 6.2	5.7 5.3
REM Latency (min)	Mean S.D.	155.8 47.0	128.6 69.1	126.2 51.8	110.6 45.1	97.7 42.9
Number of Arousals	Mean S.D.	29.3 10.7	50.9 18.9	43.8 14.5	49.0 7.3	25.8 8.4
% Stage W †	Mean S.D.	23.8 22.9	21.0 15.2	13.8 5.5	16.0 6.5	7.8 2.8
% Stage 1	Mean S.D.	6.1 3.9	7.6 4.6	5.6 2.9	6.0 4.6	3.9 1.6
% Stage 2	Mean S.D.	61.6 6.5	69.0 5.9	71.7 8.7	68.1 7.9	56.3 5.4
% Stage 3	Mean S.D.	5.9 1.5	5.2 2.6	6.1 3.0	5.7 2.2	6.5 2.1
% Stage 4	Mean S.D.	12.2 5.4	0.6 1.1	0.3 0.7	0.2 0.4	14.9 6.1
% Stage REM	Mean S.D.	14.2 3.3	17.6 2.8	18.8 5.8	20.2 5.6	18.4 3.5

* 1 = baseline night; 2 , 3 , 4 = delta wave sleep interuption; 5 = recovery night

† W = wake

TABLE 4: Percent Stage 4 Sleep During DWSI.

Interruption nights	Moldofsky	GRP2	GRP3
1	0.8	2.2	0.6
2	3.1	3.2	0.3
3	2	1.9	0.2
Average:	2	2.4	0.4

TABLE 5: Dolorimetry Score Ratios †

Group	Overnight DSR		Across Study DSR	
	mean	SD	mean	SD
GRP1	0.88	0.07	1.11	0.22
GRP2	0.98	0.05	1.01	0.16
GRP3	0.78	0.18	0.92	0.1

† see text for definition of ratios. Values less than one indicate increased pain sensitivity.