

Am J Med. 2012 May;125(5):S1.

**Managing chronic pain with nonopioid analgesics: a multidisciplinary consult.**

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**Abstract**

As detailed in this online CME activity ([www.cmeaccess.com/AJM/ChronicPain04](http://www.cmeaccess.com/AJM/ChronicPain04) - registration required), determining pain mechanism is an important aspect guiding treatment selection for chronic musculoskeletal pain states.

Although broad classifications provide a framework, any combination of mechanisms may be present in a chronic pain patient, and there is growing evidence that pain states generally considered nociceptive may also involve elements of augmented central nervous system pain processing.

Nonopioid analgesics, including serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and alpha-2-delta ligand anticonvulsants, are the treatments of choice for fibromyalgia and other central neuropathic pain states.

Additionally, studies have now shown that certain SNRIs can be effective in treating "classic" nociceptive pain states, such as osteoarthritis, and also are effective for low back pain. In addition to considering biological mechanisms, chronic pain management also involves recognizing and evaluating the contribution of psychological and sociocultural factors that can influence pain chronicity and patient prognosis.

A multimodal/multidisciplinary approach incorporating pharmacologic and nonpharmacologic therapy into a program that includes more than one discipline is important to improve outcomes in patients with chronic pain.

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### **Prevalence of Fibromyalgia Among Patients With Chronic Hepatitis C Infection: Relationship to Viral Characteristics and Quality of Life**

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#### *Abstract*

**Objectives:** We determined the prevalence of fibromyalgia syndrome (FMS) in a cohort of subjects with chronic hepatitis C virus (HCV), and the relationship to subject demographics, viral characteristics, and quality of life.

**Methods:** In a cross-sectional study of a cohort of HCV-infected individuals, all subjects underwent a standard assessment including history, clinical examination, and functional assessments for pain and disability.

**Results:** A total of 185 subjects met the inclusion criteria. Median age was 48.7 years, and 110 (59%) were women. A total of 106 (57%) of the subjects met criteria for the presence of FMS. Widespread pain and  $\geq 11$  tender points were present in all of the subjects with FMS, fatigue in 98 (92%), and depression in 60 (57%). Among those with FMS, mean pain score was  $70 \pm 11.78$  and 36% reported some functional impairment on (HAQ-DI $>0$ ), with 17% reporting moderate-to-severe functional impairment (HAQ-DI $\geq 1.5$ ). Compared to subjects who did not meet criteria for fibromyalgia, patients with fibromyalgia were more likely to be older, females, living alone, smokers, have a history of depression, had acquired HCV via a blood transfusion, and had HCV genotype-1 (table 1,  $p < 0.005$  for all categories).

**Conclusions:** This study reveals a high prevalence of FMS (57%) among subjects with chronic HCV infection, one third of whom reported some degree of functional impairment. Recognition and management of this condition in such patients will help improve their quality of life.

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Abstracts of the XXII World Allergy Congress: ASTHMA AND CO-MORBID CONDITIONS

### 312 Medication Responses in Chronic Fatigue Syndrome (CFS) and Non-CFS Subjects

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#### *Abstract*

**Background:** There is a clinical perception that Chronic Fatigue Syndrome (CFS) subjects have greater drug sensitivity and "allergy" than the rest of the population. This perception was tested by assessing the symptoms associated with medication use in a group stratified by CFS status and gender.

**Methods:** 194 subjects answered a binary (yes-no) questionnaire (Simon GE et al, 1993) to determine if "medications" (not further subdivided by drug class) caused any of 25 symptoms from the neurological (6 symptoms); musculoskeletal (5); airways (7); gastrointestinal (5); and skin (2) systems. Subjects used our CFS Severity score to estimate the severity of fatigue and the 8 minor criteria for the previous 6 months.

**Results:** The subgroup of ALL CFS females had more frequent nausea (32% vs 13%;  $P = 0.013$ ) and visual changes (19% vs 4%;  $P = 0.018$ ) than ALL non-CFS females. ALL CFS males had nausea (26%;  $P = 0.003$ ) and dizziness (23%;  $P = 0.006$ ) compared to zero in ALL non-CFS males.

However, these differences were misleading because many individuals had no symptoms, and so would not have adverse complaints or contact their physicians. Therefore, the 47% of CFS and 72% of non-CFS subjects with zero symptoms were removed.

The remaining 65 CFS subjects had 5.6 symptoms (95% CI, 4.2- 7.0). The 20 non-CFS subjects had 3.5 symptoms (1.8 to 5.2; not significant by t test). Females in these subsets had no significant differences in symptoms frequencies. However, CFS males ( $n = 22$ ) had more nausea (54.5% vs 0%;  $P = 0.067$ ) and dizziness (50% vs 0%;  $P = 0.091$ ) for non-CFS males ( $n = 4$ ).

**Conclusions:** The apparent higher prevalence of medication-related symptoms in CFS than non-CFS was biased by the large number of subjects with zero symptoms. When subjects with no complaints were excluded, there was no difference between CFS and non-CFS females, but a trend for CFS males to have had more gastrointestinal and neurologic symptoms than the non-CFS males.

Overall, the equivalence of symptoms in CFS and non-CFS suggests that Multiple Chemical Sensitivity (MCS) may be an independent syndrome. These methods will direct our analysis of other irritants in this multiple chemical sensitivity questionnaire.

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### **Reliability and Validity of a Low Load Endurance Strength Test for Upper and Lower Extremities in Patients With Fibromyalgia.**

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#### *Abstract*

**OBJECTIVE:** To evaluate the reliability, standard error of the mean (SEM), clinical significant change, and known group validity of 2 assessments of endurance strength to low loads in patients with fibromyalgia syndrome (FS).

**DESIGN:** Cross-sectional reliability and comparative study.

**PARTICIPANTS:** Middle-aged women with FS (n=95) and healthy women (n=64) matched for age, weight, and body mass index (BMI) were recruited for the study.

**MAIN OUTCOME MEASURES:** The endurance strength to low loads tests of the upper and lower extremities and anthropometric measures (BMI) were used for the evaluations. The differences between the readings (tests 1 and 2) and the SDs of the differences, intraclass correlation coefficient (ICC) model (2,1), 95% confidence interval for the ICC, coefficient of repeatability, inpatient SD, SEM, Wilcoxon signed-rank test, and Bland-Altman plots were used to examine reliability. A Mann-Whitney U test was used to analyze the differences in test values between the patient group and the control group. We hypothesized that patients with FS would have an endurance strength to low loads performance in lower and upper extremities at least twice as low as that of the healthy controls.

**RESULTS:** Satisfactory test-retest reliability and SEMs were found for the lower extremity, dominant arm, and nondominant arm tests (ICC=.973-.979;  $P<.001$ ; SEMs=1.44-1.66 repetitions). The differences in the mean between the test and retest were lower than the SEM for all performed tests, varying from -.10 to .29 repetitions. No significant differences were found between the test and retest ( $P>.05$  for all).

The Bland-Altman plots showed 95% limits of agreement for the lower extremity (4.7 to -4.5), dominant arm (3.8 to -4.4), and nondominant arm (3.9 to -4.1) tests. The endurance strength to low loads test scores for the patients with FS were 4-fold lower than for the controls in all performed tests ( $P<.001$  for all).

**CONCLUSIONS:** The endurance strength to low loads tests showed good reliability and known group validity and can be recommended for evaluating endurance strength to low loads in patients with FS. For individual evaluation, however, an improved score of at least 4 and 5 repetitions for the upper and lower extremities, respectively, was required for the differences to be considered as substantial clinical change. Patients with FS showed impaired endurance strength to low loads performance when compared with the general population.

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**Fibromyalgia syndrome and chronotype: late chronotypes are more affected.**

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**Abstract**

Sleep has strong links to the symptomology of fibromyalgia syndrome (FMS), a diffuse musculoskeletal pain disorder. Information about the involvement of the circadian clock is, however, sparse.

In this study, 1548 individuals with FMS completed an online survey containing questions on demographics, stimulant consumption, sleep quality, well-being and subjective pain, chronotype (assessed by the Munich ChronoType Questionnaire, MCTQ), and FMS impact. Chronotype (expressed as the mid-sleep-point on free days, corrected for sleep deficit on workdays, MSF(sc)) significantly correlated with stress-ratings, so-called "memory failures in everyday life," fatigue, FMS impact, and depression but not with anxiety.

When chronotypes were categorized into 3 groups (early, intermediate, late), significant group differences were found for sum scores of perceived stress, memory failures in everyday life, fatigue, FMS impact, and depression but not anxiety, with late chronotypes being more affected than early chronotypes.

Sleepiness ratings were highest in early chronotypes. Challenges of sleep quality and subjective pain were significantly increased in both early and late chronotypes. The results show that according to their reports, late chronotypes are more affected by fibromyalgia.

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Am J Phys Med Rehabil. 2012 Mar 29. [Epub ahead of print]

**Effects of Exercise Training and Detraining in Patients with Fibromyalgia Syndrome: A 3-Yr Longitudinal Study.**

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*Abstract*

**OBJECTIVE:** This study aimed to evaluate the immediate effects of a 6-mo combined exercise program on quality-of-life, physical function, depression, and aerobic capacity in women with fibromyalgia syndrome and to determine the impact of repeated delivery of the intervention.

**DESIGN:** Forty-one women with fibromyalgia were randomly assigned to a training group (EG; n = 21) and a control group (CG; n = 20). Quality-of-life and physical function were assessed using the 36-item Short-Form Health Survey (SF-36) and the Fibromyalgia Impact Questionnaire, and depression was measured using the Beck Depression Inventory. Physical fitness was measured using the 6-min Walk Test. Outcomes were assessed at baseline and after each 6-mo intervention, which was delivered over 30 mos (6 mos of training and 6 mos of detraining).

**RESULTS:** After a 6-mo combined exercise program, there was a significant improvement in the Fibromyalgia Impact Questionnaire ( $P < 0.0005$ ) for the training group over the control group. Repeated-measures analysis of variance across all time points demonstrated significant main effects for time for the Fibromyalgia Impact Questionnaire, SF-36, Beck Depression Inventory and the 6-min Walk Test, but there were no between-group interaction effects.

For the EG, there were significant within-group changes in the Fibromyalgia Impact Questionnaire, SF-36, and Beck Depression Inventory at the final time point; however, there were no within-group changes for the control group. Improvement achieved for the training group were maintained during the detraining period.

**CONCLUSIONS:** A long-term exercise program can produce immediate improvements in key health domains in women with fibromyalgia. The benefits achieved with regular training can be maintained for 30 mos. The lack of difference between groups over time may be caused by attrition and consequent lack of power at the final time point.

**Subjective sleep quality and daytime sleepiness in a large sample of patients with chronic fatigue syndrome (CFS).**

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**Abstract**

Chronic fatigue syndrome (CFS) is characterised by incapacitating fatigue in combination with a number of minor criteria, including unrefreshing sleep without further specifications, in the absence of psychiatric and internal disease. As little data exist on subjective sleep quality and daytime sleepiness, these parameters were assessed in a large sample of CFS patients.

Consecutive patients with a diagnosis of CFS in a tertiary referral centre filled out the Fatigue Questionnaire (FQ), Medical Outcomes Study 36-Item Short Form Health Survey (MOS SF-36), Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI).

Inclusion comprised 415 individuals (mean age 40.5 yr, SD 7.9, range 18-64; 86% female). Mean FQ (26.90; SD 4.04), mean Global Physical Health from the MOS SF-36 (29.30; SD 12.25) and Global Mental Health from the MOS SF-36 (49.62; SD 18.31) scores corresponded with literature data for similar CFS samples.

High mean ESS (10.51; SD 5.52) and global PSQI (10.17; SD 4.02) were observed. No significant relationship was found between ESS and global PSQI.

In contrast, regression analysis demonstrated a significant cubic relation between ESS and 'PSQI without daytime dysfunction'. A subgroup (n=69) with an insomnia-like phenotype low ESS (<5), high PSQI (mean 11.51; SD 3.86) was observed.

The assessment of subjective sleep quality and daytime sleepiness in a large sample of CFS patients indicated high mean PSQI and ESS values. ESS and 'PSQI without daytime dysfunction' were inversely related at the spectral ends of ESS. A distinct subgroup with clinical features of insomnia was identified.

\* The ESS measures daytime sleepiness which may be appropriate for narcolepsy for example, but many not be directly correlated with fatigue levels. Neu et al 2008 concluded, "Despite possible overlap in symptoms and signs ... our data indirectly support the clinical distinction between fatigue and sleepiness.

<http://www.novasleepcenter.com/documents/EPWORTHSLEEPINESSSCALE..09...>

\* The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Because symptoms tend to wax and wane in ME and CFS, one month may not be sufficient to accurately measure sleep quality. Nineteen individual items generate seven "component" scores:

subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score.

[http://consultgerirn.org/uploads/File/trythis/try\\_this\\_6\\_1.pdf](http://consultgerirn.org/uploads/File/trythis/try_this_6_1.pdf)

World J Gastroenterol. 2012 Feb 7;18(5):445-52.

**Chronic fatigue is associated with increased disease-related worries and concerns in inflammatory bowel disease.**

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*Abstract*

**AIM:** To investigate the impact of chronic fatigue on disease-related worries in inflammatory bowel disease (IBD) and the potential multicollinearity between subjective questionnaires.

**METHODS:** Patients in remission or with mild-to-moderate disease activity completed the fatigue questionnaire (FQ), the rating form of IBD patient concerns (RFIPC), the Short-Form 36 (SF-36), and IBD questionnaire (N-IBDQ). In addition, clinical and epidemiological data were obtained.

**RESULTS:** In total, 140 patients were included; of which 92 were diagnosed with ulcerative colitis and 48 with Crohn's disease. The mean age of patients with chronic fatigue was 44.2 years (SD = 15.8) and for non-fatigued patients was 44.7 years (SD = 16.0).

Chronic fatigued patients had clinically significantly increased levels of disease-related worries, as measured by Cohen's d effect size. Worries about having an ostomy bag, loss of bowel control, and energy levels were most prominent in both chronic fatigued and non-chronic fatigued IBD patients.

Variance inflation factor (VIF) and tolerance indicated that there were no problematic multicollinearity among the FQ, RFIPC, SF-36 and N-IBDQ responses (VIF < 5 and tolerance > 2).

**CONCLUSION:** Chronic fatigue is associated with increased levels of disease-related worries and concerns in IBD. Increased levels of worries were also associated with impaired health-related quality of life.

J Pain. 2012 Apr;13(4):390-400.

**Effective connectivity among brain regions associated with slow temporal summation of C-fiber-evoked pain in fibromyalgia patients and healthy controls.**

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**Abstract**

Temporal summation of "second pain" (TSSP) or "windup" results from the summation of C-fiber-evoked responses of dorsal-horn neurons. This phenomenon is dependent on stimulus frequency ( $\geq 33$  Hz) and relevant to central sensitization and chronic pain.

Our previous neuroimaging studies characterized brain regions associated with TSSP in normal control (NC) and fibromyalgia (FM) groups. During an fMRI scan, subjects received sensitivity-adjusted repetitive heat pulses at .33 on the right foot. FM subjects required significantly lower stimulus intensities than NC to achieve similar TSSP and no significant group differences in the pain-related brain activity were detected.

In our current study, we asked whether the effective connectivity among a set of TSSP-related brain regions identified in our previous work differs amongst FM and NC groups.

Structural equation modeling was used to characterize the effective connectivity amongst a priori selected brain areas, including the thalamus, S1, S2, posterior insula, and the anterior midcingulate cortex (aMCC) within the left and right hemispheres.

This analysis confirmed our a priori models of effective connectivity among these regions mainly confirmed those hypothesized, yet some unpredicted connections were additionally identified (thalamus to aMCC and aMCC to S1).

While the models of effective connectivity were not identical in the FM and NC groups, they were very similar. Additionally, the TSSP related effective connectivity of right and left hemisphere regions was very similar. These results provide evidence for significant overlap of the fundamental brain mechanisms that process sensory and affective information related to TSSP in NC and FM groups.

**PERSPECTIVE:** Models of effective connectivity involving pain-related processes were estimated with fMRI data from chronic pain and healthy populations. Models were estimated in both hemispheres, and although similar, fibromyalgia was associated with unique models of pain-related processes. Group differences involved the left hemisphere and S1, S2, and posterior insula.

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**Time-course of antibody responses against *Coxiella burnetii* following acute Q fever.**

Teunis PF, Schimmer B, Notermans DW, Leenders AC, Wever PC, Kretzschmar ME, Schneeberger PM., Centre for Infectious Disease Control, Epidemiology and Surveillance Unit, RIVM, Bilthoven, The Netherlands.

**Abstract**

**SUMMARY:** Large outbreaks of Q fever in The Netherlands have provided a unique opportunity for studying longitudinal serum antibody responses in patients.

Results are presented of a cohort of 344 patients with acute symptoms of Q fever with three or more serum samples per patient.

In all these serum samples IgM and IgG against phase 1 and 2 *Coxiella burnetii* were measured by an immunofluorescence assay. A mathematical model of the dynamic interaction of serum antibodies and pathogens was used in a mixed model framework to quantitatively analyse responses to *C. burnetii* infection.

Responses show strong heterogeneity, with individual serum antibody responses widely different in magnitude and shape. Features of the response, peak titre and decay rate, are used to characterize the diversity of the observed responses.

Binary mixture analysis of IgG peak levels (phases 1 and 2) reveals a class of patients with high IgG peak titres that decay slowly and may represent potential chronic cases.

When combining the results of mixture analysis into an odds score, it is concluded that not only high IgG phase 1 may be predictive for chronic Q fever, but also that high IgG phase 2 may aid in detecting such putative chronic cases.

The FASEB Journal. 2012;26:1035.20) © 2012 FASEB 1035.20

**Decreased basal ganglia activation in Chronic Fatigue Syndrome subjects is associated with increased fatigue**

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**Objectives:** Conduct a functional magnetic resonance (fMRI) study using a monetary win-lose gambling task that strongly activates basal ganglia to test hypothesis of decreased basal ganglia function in chronic fatigue syndrome (CFS).

**Methods:** Participants included 18 CFS subjects (1994 case definition) and 41 non-fatigued controls matched on age, sex and race who were free of psychotropic medications and significant depression (Zung Depression score <60).

The general activation pattern for win-lose contrast across all subjects was determined. The resulting statistical parametric brain map thresholded at  $p < 0.05$ , corrected for multiple comparisons, was intersected with basal ganglia regions of interest (ROIs). For each subject, the average value of win-lose activation contrast in each ROI was extracted.

**Results:** CFS subjects showed decreased right caudate ( $p = 0.01$ ) and right globus pallidus ( $p = 0.02$ ) activation compared to controls. The decreased globus pallidus activation correlated with increased mental fatigue ( $r^2 = 0.49$ ,  $p = 0.001$ ), general fatigue ( $r^2 = 0.34$ ,  $p = 0.01$ ) and reduced activity ( $r^2 = 0.29$ ,  $p = 0.02$ ) Multidimensional Fatigue Inventory scores of CFS subjects but not controls.

**Conclusion:** Reduced basal ganglia activation may contribute to symptoms of fatigue in CFS subjects.

The findings in this report are those of the authors and do not necessarily reflect the views of the funding agency (CDC).

Psychiatry Res. 2012 Apr 20. [Epub ahead of print]

**Myalgic Encephalomyelitis (ME), Chronic Fatigue Syndrome (CFS), and Chronic Fatigue (CF) are distinguished accurately: Results of supervised learning techniques applied on clinical and inflammatory data.**

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**Abstract**

There is much debate on the diagnostic classification of Myalgic Encephalomyelitis (ME), Chronic Fatigue Syndrome (CFS) and chronic fatigue (CF). Post-exertional malaise (PEM) is stressed as a key feature.

This study examines whether CF and CFS, with and without PEM, are distinct diagnostic categories.

Fukuda's criteria were used to diagnose 144 patients with chronic fatigue and identify patients with CFS and CF, i.e. those not fulfilling the Fukuda's criteria. PEM was rated by means of a scale with defined scale steps between 0 and 6. CFS patients were divided into those with PEM lasting more than 24h (labeled: ME) and without PEM (labeled: CFS).

The 12-item Fibromyalgia and Chronic Fatigue Syndrome (FF) Rating Scale was used to measure severity of illness. Plasma interleukin-1 (IL-1), tumor necrosis factor (TNF) $\alpha$ , and lysozyme, and serum neopterin were employed as external validating criteria. Using fatigue, a subjective feeling of infection and PEM we found that ME, CFS, and CF were distinct categories.

Patients with ME had significantly higher scores on concentration difficulties and a subjective experience of infection, and higher levels of IL-1, TNF $\alpha$ , and neopterin than patients with CFS. These biomarkers were significantly higher in ME and CFS than in CF patients. PEM loaded highly on the first two factors subtracted from the data set, i.e. "malaise-sickness" and "malaise-hyperalgesia".

Fukuda's criteria are adequate to make a distinction between ME/CFS and CF, but ME/CFS patients should be subdivided into ME (with PEM) and CFS (without PEM).

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Pain Res Manag. 2012 Mar-Apr;17(2):89-92.

**Evaluation of leptin levels among fibromyalgia patients before and after three months of treatment, in comparison with healthy controls.**

Ablin JN, Aronov N, Shimon I, Kanety H, Pariente C, Aloush V, Elkayam O, Levartovsky D.

*Abstract*

**BACKGROUND:** Leptin, an adipocyte-produced cytokine, interacts with various hormones, including those of the hypothalamic-pituitary-adrenal axis. Fibromyalgia is a syndrome characterized by widespread pain accompanied by tenderness. The pathogenesis involves a disturbance in pain processing and transmission by the central nervous system, leading to a general increase in pain perception.

**OBJECTIVES:** To analyze potential changes in leptin levels among female fibromyalgia patients compared with healthy controls, and to evaluate the changes in leptin levels during treatment.

**METHODS:** Sixteen female fibromyalgia patients were recruited. Patients underwent clinical evaluation, physical examination, including manual dolorimetry, and were evaluated regarding quality of life, pain, fatigue, anxiety and depression. Plasma leptin levels were determined by ELISA. Patients were offered standard treatment for fibromyalgia. Clinical evaluation and leptin determination were repeated after three months.

**RESULTS:** No significant difference was observed between leptin levels among fibromyalgia patients and controls; no significant correlation was observed between leptin levels and clinical parameters reflecting fibromyalgia severity; and no significant change was observed in leptin levels over three months of treatment. These results did not change after adjustment of leptin levels for body mass index values.

**CONCLUSIONS:** The results of the present study do not support the existence of a significant relationship between leptin and fibromyalgia pathogenesis. Increasing the sample size or examining the interaction between leptin and additional hormones/mediators of metabolism and body weight control may yet uncover significant information in this field.

Emerg Infect Dis. 2012 May;18(5):783-91. doi: 10.3201/eid1805.111366.

### **Bartonella spp. Bacteremia and Rheumatic Symptoms in Patients from Lyme Disease-endemic Region.**

Maggi RG, Mozayani BR, Pultorak EL, Hegarty BC, Bradley JM, Correa M, Breitschwerdt EB.

#### **Abstract**

*Bartonella* spp. infection has been reported in association with an expanding spectrum of symptoms and lesions.

For this cross-sectional study, we enrolled only patients examined by a rheumatologist in the Maryland–Washington, DC, USA, area from August 25, 2008, through April 1, 2009. Because *Bartonella* spp. are known to primarily infect cells within the vascular system, including erythrocytes, endothelial cells, and potentially circulating and tissue macrophages (1,5,6), selection was biased by patients who had historical, physical examination, or laboratory evidence of small vessel disease, including a subset of patients with a prior diagnosis of Lyme disease or chronic post–Lyme syndrome. We also included patients with chronic joint pain, prior documentation of synovial vascular inflammation, or a diagnosis of rheumatoid arthritis. Among 296 patients examined by a rheumatologist, prevalence of antibodies against *Bartonella henselae*, *B. koehlerae*, or *B. vinsonii* subsp. *berkhoffii* (185 [62%]) and *Bartonella* spp. bacteremia (122 [41.1%]) was high.

Conditions diagnosed before referral included Lyme disease (46.6%), arthralgia/arthritis (20.6%), chronic fatigue (19.6%), and fibromyalgia (6.1%). However, the diagnostic criterion upon which these infections were based was not available for review because all prior diagnoses were self-reported. Overall, 185 (62.5%) of 296 patients had antibodies to *B. henselae*, *B. koehlerae*, or *B. vinsonii* subsp. *berkhoffii*, and 122 (41.1%) were positive for *Bartonella* spp. according to PCR. In most instances, DNA sequencing of the amplified product facilitated identification of the infecting species. The prevalence of antibodies against *Bartonella* spp. (93 [67.4%]) and bacteremia [57 [1.3%]) among 138 patients with a prior diagnosis of Lyme disease did not differ from that of the overall study population.

Because our analysis was restricted to patients selected by a rheumatologist practicing in a Lyme disease–endemic region, extrapolations to other regions or other rheumatology practices might not be applicable.

*B. henselae* bacteremia was significantly associated with prior referral to a neurologist, most often for blurred vision, subcortical neurologic deficits, or numbness in the extremities, whereas *B. koehlerae* bacteremia was associated with examination by an infectious disease physician.

This cross-sectional study cannot establish a causal link between *Bartonella* spp. infection and the high frequency of neurologic symptoms, myalgia, joint pain, or progressive arthropathy in this population; however, the contribution of *Bartonella* spp. infection, if any, to these symptoms should be systematically investigated.

The full study can be read here: <http://wwwnc.cdc.gov/eid/article/18/5/pdfs/11-1366.pdf>

Cochrane Database Syst Rev. 2012 Apr 18;4:CD009807.

### **Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome.**

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#### *Abstract*

**BACKGROUND:** Fibromyalgia (FM) syndrome is a chronic condition of unknown aetiology characterised by musculoskeletal pain that often co-exists with sleep disturbance, cognitive dysfunction and fatigue. Patients often report high disability levels and poor quality of life. Since there is no specific treatment that alters the pathogenesis of FM, drug therapy focuses on pain reduction and improvement of other bothersome symptoms.

**OBJECTIVES:** The objective of this review was to assess the effectiveness and safety of monoamine oxidase inhibitors (MAOIs) in the treatment of FM syndrome.

**SEARCH METHODS:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 10), MEDLINE (1966 to November 2010), EMBASE (1980 to November 2010) and the reference lists of reviewed articles.

**SELECTION CRITERIA:** We selected all randomised, double-blind trials of MAOIs used for the treatment of FM pain in adult participants.

**DATA COLLECTION AND ANALYSIS:** Two authors assessed risk of bias and extracted data independently onto a specially designed pro forma and a third review author cross-checked them.

**MAIN RESULTS:** We included two studies of inconsistent risk of bias with a total of 230 patients diagnosed with FM. We evaluated two MAOIs: pirlindole and moclobemide. Pirlindole showed statistically significant results compared with placebo for several outcomes (pain, tender points and overall assessment by the patient and the physician), whereas moclobemide did not show statistically significant differences between groups.

Pooled results of the two studies displayed a modest effect size in pain (mean difference (MD) -1.45 (121 patients; 95% confidence interval (CI) -2.71 to -0.20; number needed to treat (NNT) 2 (95% CI 1 to 12); I(2) = 59%), implying a minimal clinically important difference (MCID) and a small effect on tender points (standardised mean difference (SMD) -0.36 (121 patients; 95% CI -0.72 to -0.00; I(2) = 31%).

No effect was seen on global assessment by patient. Physical function and sleep disturbance were not measured. The most frequent adverse events were nausea and vomiting, with statistically significant differences between groups (risk ratio (RR) 7.82 (89 patients; 95% CI 1.02 to 59.97; NNT 7 (95% CI 4 to 33)).

**AUTHORS' CONCLUSIONS:** Data suggest that the effectiveness of MAOIs for the treatment of FM symptoms is limited. Although we observed a moderate effect size on pain and a small one on tender points, these results should be taken with caution as they are only based on two studies with a small number of patients and inconsistent risk of bias among them.

Altern Ther Health Med. 2012 Jan-Feb;18(1):36-40.

**The assessment of the energy metabolism in patients with chronic fatigue syndrome by serum fluorescence emission.**

Mikirova N, Casciari J, Hunninghake R.

**Abstract**

**Context** Chronic fatigue syndrome (CFS) is a debilitating fatigue illness that has unknown etiology and lacks an objective diagnostic marker.

**Objective** To examine the metabolic component of CFS to determine if practitioners can use serum NAD(P)H concentration measurements to monitor metabolism and fatigue status in patients with CFS.

**Design** The research team conducted a case-control study, comparing a group of patients who were diagnosed with CFS with a control group of healthy subjects. The team obtained venous blood samples from fasting patients to examine the serum NAD(P)H concentrations.

**Setting** The study occurred at the Riordan Clinic in Wichita, Kansas.

**Participants** The study included 44 CFS patients at the Riordan Clinic and 30 healthy control participants. The CFS patients presented a spectrum of symptoms that had existed for at least 6 months: new, unexplained, persistent, or relapsing chronic fatigue that bed rest did not resolve and that was severe enough to reduce daily activity significantly by 50% in conjunction with headache, muscle pain, pain in multiple joints, and unrefreshing sleep. In the control group, the research team enrolled subjects without diagnosis of disease or injury.

**Outcome Measures** The research team determined levels of serum reduced nicotinamide adenine dinucleotides (NADH and NAD[P]H) by measuring serum fluorescence emission at 450 nm. The team then conducted sensitivity and specificity analyses. Results NAD(P)H concentrations in serum of CFS participants averaged  $8.0 \pm 1.4$  (standard deviation [SD]) nmol/mL, while those in the healthy controls averaged  $10.8 \pm 0.8$  (SD) nmol/mL, a statistically significant difference.

Using a cut-off concentration of 9.5 nmol/mL, the research team attained a sensitivity of 0.73 and a specificity of 1.0. An analysis of receiver-operator characteristics yielded an area under the curve of 0.9.

The research team compared serum NAD(P)H to several endocrine and metabolic lab parameters.

Serum NAD(P)H was directly correlated with serum CoQ10 levels and inversely correlated with urine hydroxyhemopyrrolin-2-one levels.

**Conclusions Based on these findings**, the research team proposed using serum NAD(P)H, measured as an intrinsic serum-fluorescence emission, to monitor metabolism and fatigue status in patients with CFS. Following patients NAD(P)H levels over time may aid in selecting therapeutic strategies and monitoring treatment outcomes. (Altern Ther Health Med. 2012;18(1):36-40.).

<http://www.riordanclinic.org/research/articles/AT-2012-v18.pdf>

Clin Rheumatol. 2012 May 2. [Epub ahead of print]

**Should rheumatologists retain ownership of fibromyalgia? A survey of Ontario rheumatologists.**

Ghazan-Shahi S, Towheed T, Hopman W., Internal Medicine, Queen's University, Kingston, Canada,

**Abstract**

Fibromyalgia is a controversial widespread chronic pain disorder that includes a wide constellation of somatic and emotional symptoms. This study surveyed the opinion of Ontario rheumatologists with respect to their beliefs about the nature and management of fibromyalgia.

A key objective was to ascertain if rheumatologists should continue to be the main care providers for these patients.

A survey comprising 13 questions was sent electronically to all 150 Ontario rheumatologists. The questionnaire was designed to obtain demographic data as well as opinions regarding different aspects of fibromyalgia. Data were analysed descriptively, and comparisons were made using chi-square tests.

A total of 80 respondents completed our survey for a completion rate of 53 %. The majority had completed their training in Canada (85 %) and had been practising for more than 15 years (50 %).

Key findings were:

- (1) 71 % believe that rheumatologists should not retain ownership of fibromyalgia,
- (2) 55 % believe that fibromyalgia is primarily a psychosomatic illness as opposed to a physical illness,
- (3) 89 % believe that the family physician should be the main care provider for these patients, and
- (4) rheumatologists who consider fibromyalgia to be a physical illness were also significantly more likely to believe that rheumatologists should retain ownership of this disease ( $p=0.023$ ) and were more likely to continue managing these patients in their practice ( $p=0.011$ ).

The majority of Ontario rheumatologists do not wish to retain ownership of fibromyalgia. However, most of them continue to manage these patients, even though they believe that the family physician should be the main care provider for patients with fibromyalgia. Rheumatologists may be providing care to these patients primarily because this care is not available to them from their primary care physicians.

PMID: 22547393 [PubMed - as supplied by publisher]

Zhen Ci Yan Jiu. 2012 Feb;37(1):38-40, 58.

**Effect of acupuncture on serum malonaldehyde content, superoxide dismutase and glutathione peroxidase activity in chronic fatigue syndrome rats.**

Liu CZ, Lei B., School of Aesthetic Medicine, Yichun College, Yichun 336000, China.

*Abstract*

**OBJECTIVE:** To study the effect of acupuncture on blood oxygen free radical metabolism in rats with chronic fatigue syndrome (CFS).

**METHODS:** Thirty male SD rats were randomly divided into control group (n = 10), model group (n = 10) and acupuncture group (n = 10). CFS model was established by repeated suspension (1.0-2.5 h) and forced cold water swimming (7 min), once daily continuously for 12 days. For rats in the acupuncture group, bilateral "Zusanli" (ST 36) and "Sanyinjiao" (SP 6) were stimulated by manipulating the acupuncture needles intermittently for 20 min, once daily, and with 7 days being a treatment course. The treatment was conducted for three courses with an interval of 3 days between two courses. Serum malonaldehyde (MDA) content, superoxide dismutase (SOD) activity, and glutathione peroxidase (GSH-PX) activity were detected by thiobarbituric acid chromatometry (TBA), xanthine oxidase (XOD) and dithio-bis-nitrobenzoic acid (DTNB), respectively.

**RESULTS:** In comparison with the control group, serum MDA content was up-regulated significantly, while serum SOD activity and GSH-PX activity were decreased considerably in the model group ( $P < 0.01$ ).

Compared with the model group, serum MDA level was down-regulated apparently, and serum SOD activity and GSH-PX activity were up-regulated remarkably in the acupuncture group ( $P < 0.01$ ).

**CONCLUSION:** Acupuncture can adjust metabolism of serum oxygen free radicals in CFS rats, which probably contributes to its effect in relieving CFS in clinic.

PubMed, J Affect Disord. 2012 May 7. [Epub ahead of print]

**Cytotoxic lymphocyte microRNAs as prospective biomarkers for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis.**

Brenu EW, Ashton KJ, van Driel M, Staines DR, Peterson D, Atkinson GM, Marshall-Gradisnik SM., Faculty of Health Science and Medicine, Population Health and Neuroimmunology Unit, Bond University, Robina, Queensland, Australia; Faculty of Health Science and Medicine, Bond University, Robina, Queensland, Australia.

*Abstract*

**BACKGROUND:** Immune dysfunction associated with a disease often has a molecular basis. A novel group of molecules known as microRNAs (miRNAs) have been associated with suppression of translational processes involved in cellular development and proliferation, protein secretion, apoptosis, immune function and inflammatory processes.

MicroRNAs may be implicated in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), where immune function is impaired. The objective of this study was to determine the association between miRNAs in cytotoxic cells and CFS/ME.

**METHODS:** Natural Killer (NK) and CD8(+)T cells were preferentially isolated from peripheral blood mononuclear cells from all participants (CFS/ME, n=28; mean age=41.8±9.6years and controls, n=28; mean age=45.3±11.7years), via negative cell enrichment.

Following total RNA extraction and subsequent synthesis of cDNA, reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) was used to determine the expression levels of nineteen miRNAs.

**RESULTS:** There was a significant reduction in the expression levels of miR-21, in both the NK and CD8(+)T cells in the CFS/ME sufferers.

Additionally, the expression of miR-17-5p, miR-10a, miR-103, miR-152, miR-146a, miR-106, miR-223 and miR-191 was significantly decreased in NK cells of CFS/ME patients in comparison to the non-fatigued controls.

**LIMITATIONS:** The results from these investigations are not yet transferable into the clinical setting, further validity studies are now required.

**CONCLUSIONS:** Collectively these miRNAs have been associated with apoptosis, cell cycle, development and immune function. Changes in miRNAs in cytotoxic cells may reduce the functional capacity of these cells and disrupt effective cytotoxic activity along with other immune functions in CFS/ME patients.

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Psychol Med. 2012 May 9:1-6. [Epub ahead of print]

**Cognitions, behaviours and co-morbid psychiatric diagnoses in patients with chronic fatigue syndrome.**

Cella M, White PD, Sharpe M, Chalder T., Institute of Psychiatry, King's College London, UK.

*Abstract*

**BACKGROUND:** Specific cognitions and behaviours are hypothesized to be important in maintaining chronic fatigue syndrome (CFS). Previous research has shown that a substantial proportion of CFS patients have co-morbid anxiety and/or depression.

This study aims to measure the prevalence of specific cognitions and behaviours in patients with CFS and to determine their association with co-morbid anxiety or depression disorders.

**Method:** A total of 640 patients meeting Oxford criteria for CFS were recruited into a treatment trial (i.e. the PACE trial). Measures analysed were: the Cognitive Behavioural Response Questionnaire, the Chalder Fatigue Scale and the Work and Social Adjustment Scale. Anxiety and depression diagnoses were from the Structured Clinical Interview for DSM-IV. Multivariate analysis of variance was used to explore the associations between cognitive-behavioural factors in patients with and without co-morbid anxiety and/or depression.

**RESULTS:** Of the total sample, 54% had a diagnosis of CFS and no depression or anxiety disorder, 14% had CFS and one anxiety disorder, 14% had CFS and depressive disorder and 18% had CFS and both depression and anxiety disorders. Cognitive and behavioural factors were associated with co-morbid diagnoses; however, some of the mean differences between groups were small. Beliefs about damage and symptom focussing were more frequent in patients with anxiety disorders while embarrassment and behavioural avoidance were more common in patients with depressive disorder.

**CONCLUSIONS:** Cognitions and behaviours hypothesized to perpetuate CFS differed in patients with concomitant depression and anxiety. Cognitive behavioural treatments should be tailored appropriately.

## **Longitudinal investigation of natural killer cells and cytokines in chronic fatigue syndrome/myalgic encephalomyelitis**

### **Abstract**

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is an etiologically unexplained disorder characterised by irregularities in various aspects of the immunological function. Presently, it is unknown whether these immunological changes remain consistent over time.

This study investigates Natural Killer (NK) cell cytotoxic activity, NK cell subsets (CD56brightCD16- and CD56dimCD16+) and cytokines, over the course of a 12 month period in patients with CFS/ME.

**Methods:** The participants in the study comprised 65 (47.2±11.5 years) CFS/ME participants and 21 (45.2 ±9.3 years) non-fatigued controls. Flow cytometry protocols were used to assess NK subsets and NK cytotoxic activity at various time points that included baseline (T1), 6 (T2) and 12 months (T3).

Cytokine secretions were measured following mitogenic stimulation of peripheral blood mononuclear cells.

**Results:** NK cytotoxic activity was significantly decreased in the CFS/ME patients at T1, T2 and T3 compared to the non-fatigued group. Additionally, in comparison to the non-fatigued controls, the CFS/ME group had significantly lower numbers of CD56brightCD16- NK cells at both T1 and T2.

Interestingly, following mitogenic stimulation, cytokine secretion revealed significant increases in IL-10, IFN-gamma and TNF-alpha at T1 in the CFS/ME group. A significant decrease was observed at T2 in the CFS/ME group for IL-10 and IL-17A while at T3, IL-2 was increased in the CFS/ME group in comparison to the non-fatigued controls.

Overall cytotoxic activity was significantly decreased at T3 compared to T1 and T2. CD56brightCD16- NK cells were much lower at T2 compared to the T1 and T3. IL-10 and IL-17A secretion was elevated at T2 in comparison to the T1 and T3.

**Conclusion:** These results confirm decreases in immune function in CFS/ME patients, suggesting an increased susceptibility to viral and other infections. Furthermore NK cytotoxic activity may be a suitable biomarker for diagnosing CFS/ME as it was consistently decreased during the course of the 12 months study.

Author: Ekuwa W Brenu, Mieke L van Driel, Donald R Staines, Kevin J Ashton, Sharni L Hardcastle, James Keane, Lotti Tajouri, Daniel Peterson, Sandra B Ramos, Sonya M Marshall-Gradisnik

Credits/Source: Journal of Translational Medicine 2012, 10:88

The full study can be found here: <http://www.translational-medicine.com/content/pdf/1479-5876-10-88.pdf>

Exp Clin Endocrinol Diabetes. 2012 Apr 27. [Epub ahead of print]

### **Association between Thyroid Autoimmunity and Fibromyalgia.**

Suk J, Lee J, Kim J., Department of Internal Medicine, Division of Endocrinology and Metabolism, Maryknoll Medical Center, Busan, Republic of Korea.

#### **Abstract**

Evidence exists that autoimmune thyroiditis is present in a high percentage of fibromyalgia (FM) and associated with the presence of typical symptoms of FM. However, the role of thyroperoxidase antibody (TPO Ab) in the manifestation of FM is still unclear.

The goal of this study was to investigate the prevalence of positive TPO Ab in euthyroid FM patients, and whether TPO Ab positivity is associated with the clinical manifestations in euthyroid FM patients.

Thyroid assessment was done by free T4, TSH and TPO Ab. The clinical parameters including Fibromyalgia Impact questionnaire (FIQ), pain visual analogical scale (VAS) and tender point counts were evaluated in euthyroid primary FM patients, not associated with autoimmune rheumatic disease.

The immunologic tests including rheumatoid factor and antinuclear antibody were measured. We compared the prevalence of positive TPO Ab between FM patients, and healthy controls. We also compared clinical and laboratory parameters in FM patients according to the presence of TPO Ab. 149 patients of FM, 68 healthy controls were recruited. FM patients showed higher prevalence of positive TPO Ab than healthy controls (28 out of 149 patients, 19%; 5 out of 68 healthy controls, 7%; P=0.04).

There was no difference of clinical and laboratory parameters in FM patients between 2 groups subdivided by the presence of TPO Ab.

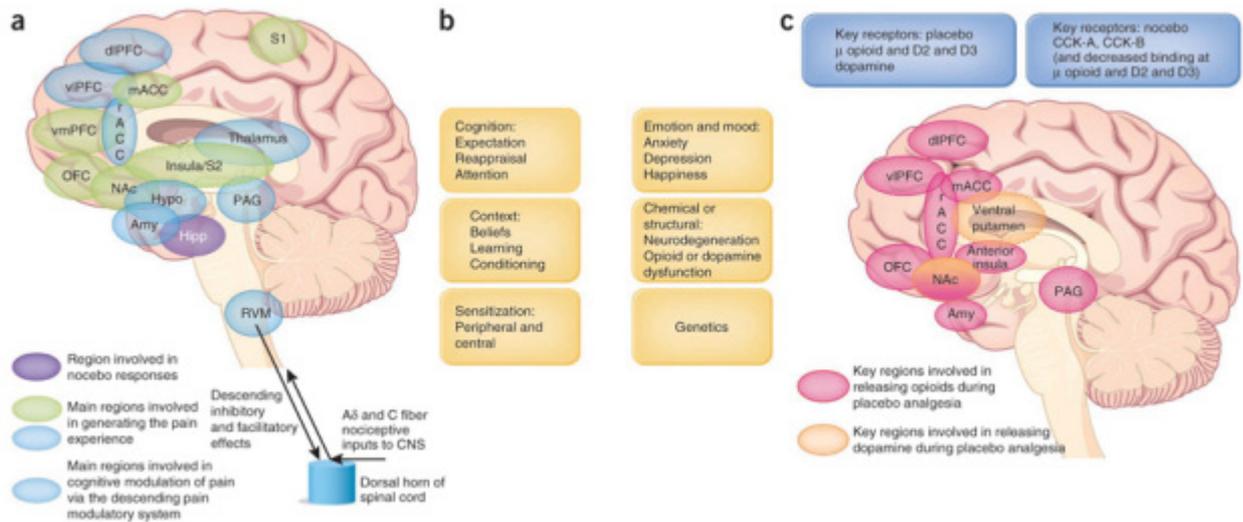
In our study, euthyroid FM patients showed significantly higher prevalence of positive TPO Ab, as compared to age and sex matched healthy control. However, TPO Ab positivity was relatively low and not associated with the clinical manifestations in euthyroid FM patients.

This finding supports [ the theory] that thyroid autoimmunity may influence the development of FM, but the evidence which supports that FM is related to autoimmune etiology is not clear, and FM severity may not be affected by the presence of thyroid autoantibody.

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Expert Rev Neurother. 2012 May;12(5):577-85.



### Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions.

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#### Abstract

The intensity of acute and chronic pain depends on interactions between peripheral impulse input and CNS pain mechanisms, including facilitation and inhibition. Whereas tonic pain inhibition is a characteristic of most pain-free individuals, pain facilitation can be detected in many chronic pain patients.

The capability to inhibit pain is normally distributed along a wide continuum in the general population and can be used to predict chronic pain. Accumulating evidence suggests that endogenous pain inhibition depends on activation of the prefrontal cortex, periaqueductal gray and rostral ventral medulla. Quantitative sensory test paradigms have been designed to acquire detailed information regarding each individual's endogenous pain inhibition and facilitation.

Such tests include: temporal summation of pain, which is mostly used to assess facilitatory pain modulation by measuring the change in pain perception during a series of identical nociceptive stimuli; and conditioned pain modulation, which tests pain inhibition by utilizing two simultaneously applied painful stimuli (the 'pain inhibits pain' paradigm).

Considerable indirect evidence seems to indicate that not only increased pain facilitation but also ineffective pain inhibition represents a predisposition for chronic pain. This view is supported by the fact that many chronic pain syndromes (e.g., fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, headache and chronic fatigue syndrome) are associated with hypersensitivity to painful stimuli and reduced endogenous pain inhibition.

However, future prospective studies will be necessary to provide definitive evidence for this relationship. Such research would not only provide important information about mechanisms relevant to chronic pain but would also permit identification of individuals at high risk for future chronic pain.

PMID: 22550986 [PubMed - in process]

J Ment Health. 2012 May 1. [Epub ahead of print]

**Sub-typing daily fatigue progression in chronic fatigue syndrome.**

Jason LA, Brown MM., Center for Community Research , DePaul University , Chicago, IL , USA.

Abstract

**Background:** Activity logs involve patients writing down their activities and symptoms over 1 or more days.

**Aims:** This study sought to classify daily fatigue patterns among patients with chronic fatigue syndrome (CFS) using activity logs.

**Method:** Fatigue intensity was self-reported every 30 min in a sample of 90 patients with CFS over 1 day. A cluster analysis using fatigue intensity, variability and slope was conducted.

**Results:** Three clusters emerged involving patients with different trajectories.

One group evidenced high fatigue intensity, low variability, and fatigue intensity stayed the same over time. A second group had moderate fatigue intensity, high variability, and fatigue intensity decreased over time.

A third group had moderate fatigue intensity, high variability, but fatigue intensity increased over time. The three clusters of patients differed on measures of actigraphy, pain and immune functioning.

**Conclusions:** Activity logs can provide investigators and clinicians with valuable sources of data for understanding patterns of fatigue and activity among patients with CFS.

PMID: 22548385 [PubMed - as supplied by publisher]

Compr Psychiatry. 2012 Apr 23. [Epub ahead of print]

**The impact of mood, anxiety, and sleep disorders on fibromyalgia.**

Consoli G, Marazziti D, Ciapparelli A, Bazzichi L, Massimetti G, Giacomelli C, Rossi A, Bombardieri S, Dell'osso L., Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie.

*Abstract*

**INTRODUCTION:** Several studies carried out mainly in North America revealed high rates of mood, anxiety and sleep disorders in patients with fibromyalgia (FM), while the information in other countries is scant.

Therefore, we aimed at investigating the prevalence and the impact of such conditions on the health-related quality of life (HRQoL) and the severity of pain in a sample of Italian FM patients.

**METHODS:** One-hundred and sixty-seven women suffering from primary FM were consecutively enrolled. Psychiatric diagnoses were made by means of DSM-IV criteria. The HRQoL and the severity of pain were measured through the Medical Outcomes Study 36-item Short-Form Health Survey (MOS-SF-36) and the FM Impact Questionnaire (FIQ).

**RESULTS:** Fibromyalgia patients showed a high rate (80.8%) of lifetime and/or current comorbidity with mood and anxiety disorders. Patients with psychiatric comorbidity resulted significantly more impaired on the Mental Component Summary score of the MOS-SF-36 and showed a higher FIQ total score than those suffering from FM only. The severity of pain was associated with current psychiatric comorbidity.

Patients with current mood disorders showed significantly lower Mental and Physical Component Summary scores of the MOS-SF-36 and higher FIQ total scores than those with current anxiety disorders or those without psychiatric comorbidity. Finally, patients with sleep disorders reported a lower HRQoL than those with a normal sleep, and specifically those with difficulty in falling in sleep had higher severity of pain.

**CONCLUSION:** Psychiatric comorbidity, in particular with mood disorders, provokes a significant impairment of the HRQoL and, when current, a higher severity of pain in FM patients.

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Mol Pain. 2012 Apr 26;8(1):32. [Epub ahead of print]

**Patients With Fibromyalgia Display Less Functional Connectivity In The Brain's Pain Inhibitory Network.**

Jensen KB, Loitole R, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Mainguy Y, Vitton O, Gracely RH, Gollub R, Ingvar M, Kong J.

**ABSTRACT:**

**BACKGROUND:** There is evidence for augmented processing of pain and impaired endogenous pain inhibition in Fibromyalgia syndrome (FM). In order to fully understand the mechanisms involved in FM pathology, there is a need for closer investigation of endogenous pain modulation.

In the present study, we compared the functional connectivity of the descending pain inhibitory network in age-matched FM patients and healthy controls (HC). We performed functional magnetic resonance imaging (fMRI) in 42 subjects; 14 healthy and 28 age-matched FM patients (2 patients per HC), during randomly presented, subjectively calibrated pressure pain stimuli. A seed-based functional connectivity analysis of brain activity was performed. The seed coordinates were based on the findings from our previous study, comparing the fMRI signal during calibrated pressure pain in FM and HC: the rostral anterior cingulate cortex (rACC) and thalamus.

**RESULTS:** FM patients required significantly less pressure (kPa) to reach calibrated pain at 50 mm on a 0-100 visual analogue scale ( $p < .001$ , two-tailed). During fMRI scanning, the rACC displayed significantly higher connectivity to the amygdala, hippocampus, and brainstem in healthy controls, compared to FM patients. There were no regions where FM patients showed higher rACC connectivity. Thalamus showed significantly higher connectivity to the orbitofrontal cortex in healthy controls but no regions showed higher thalamic connectivity in FM patients.

**CONCLUSION:** Patients with FM displayed less connectivity within the brain's pain inhibitory network during calibrated pressure pain, compared to healthy controls.

The present study provides brain-imaging evidence on how brain regions involved in homeostatic control of pain are less connected in FM patients. It is possible that the dysfunction of the descending pain modulatory network plays an important role in maintenance of FM pain and our results may translate into clinical implications by using the functional connectivity of the pain modulatory network as an objective measure of pain dysregulation.

(The FASEB Journal. 2012;26:1035.20) © 2012 FASEB 1035.20

**Decreased basal ganglia activation in Chronic Fatigue Syndrome subjects is associated with increased fatigue**

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<sup>1</sup> Centers for Disease Control and Prevention, Atlanta, GA, <sup>2</sup> Emory University School of Medicine, Atlanta, GA, <sup>3</sup> University of Modena and Reggio Emilia, Modena, Italy

**Objectives:** Conduct a functional magnetic resonance (fMRI) study using a monetary win-lose gambling task that strongly activates basal ganglia to test hypothesis of decreased basal ganglia function in chronic fatigue syndrome (CFS).

**Methods:** Participants included 18 CFS subjects (1994 case definition) and 41 non-fatigued controls matched on age, sex and race who were free of psychotropic medications and significant depression (Zung Depression score <60).

The general activation pattern for win-lose contrast across all subjects was determined. The resulting statistical parametric brain map thresholded at  $p < 0.05$ , corrected for multiple comparisons, was intersected with basal ganglia regions of interest (ROIs). For each subject, the average value of win-lose activation contrast in each ROI was extracted.

**Results:** CFS subjects showed decreased right caudate ( $p = 0.01$ ) and right globus pallidus ( $p = 0.02$ ) activation compared to controls. The decreased globus pallidus activation correlated with increased mental fatigue ( $r^2 = 0.49$ ,  $p = 0.001$ ), general fatigue ( $r^2 = 0.34$ ,  $p = 0.01$ ) and reduced activity ( $r^2 = 0.29$ ,  $p = 0.02$ ) Multidimensional Fatigue Inventory scores of CFS subjects but not controls.

**Conclusion:** Reduced basal ganglia activation may contribute to symptoms of fatigue in CFS subjects.

The findings in this report are those of the authors and do not necessarily reflect the views of the funding agency (CDC).

Explore (NY). 2012 Mar-Apr;8(2):92-8.

**A mind-body technique for symptoms related to fibromyalgia and chronic fatigue.**

Toussaint LL, Whipple MO, Abboud LL, Vincent A, Wahner-Roedler DL., Department of Psychology, Luther College, Decorah, IA 52101, USA.

**Abstract**

**CONTEXT:** A novel mind-body approach (amygdala retraining) is hypothesized to improve symptoms related to fibromyalgia and chronic fatigue.

**OBJECTIVE:** To examine the use of a mind-body approach for improving symptoms related to fibromyalgia and chronic fatigue.

**DESIGN:** This was a single-blind, randomized controlled trial.

**SETTING:** The study was conducted in a tertiary-care fibromyalgia and chronic fatigue clinic.

**PATIENTS:** Patients with fibromyalgia, chronic fatigue, or both were included.

**INTERVENTIONS:** Patients were randomly assigned to receive amygdala retraining along with standard care or standard care alone. Standard care involved attending a 1.5-day multidisciplinary program. The amygdala retraining group received an additional 2.5-hour training course in which the key tools and techniques adapted from an existing program were taught to the patient. A home-study video course and associated text were provided to supplement the on-site program. Both groups received telephone calls twice a month to answer questions related to technique and to provide support.

**MAIN OUTCOME MEASURES:** Validated self-report questionnaires related to general health, well-being, and symptoms, including Short Form-36, Measure Yourself Medical Outcome Profile, Multidimensional Fatigue Inventory, Epworth Sleepiness Scale, and Fibromyalgia Impact Questionnaire.

**RESULTS:** Of the 44 patients randomly assigned who completed baseline assessments, 21 patients completed the study (14 in the standard care group and 7 in the study group). Median age was 48 years (range, 27-56 years), and female subjects comprised 91% of the group.

Analyses demonstrated statistically significant improvements in scores for physical health, energy, pain, symptom distress, and fatigue in patients who received the amygdala retraining compared with standard care.

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<http://www.ncbi.nlm.nih.gov/pubmed/22583968>

Clin Chim Acta. 2012 May 11. [Epub ahead of print]

**Visible and near-infrared spectra collected from the thumbs of patients with chronic fatigue syndrome for diagnosis.**

Sakudo A, Kuratsune H, Kato YH, Ikuta K., SourceDepartment of Virology, Center for Infectious Disease Control, Research Institute for Microbial Diseases, Osaka University, Yamadaoka, Suita, Osaka 565-0871, Japan; Fatigue Clinical Center, 21st Century COE Program, Osaka City University Graduate School of Medicine, Abeno-ku, Osaka 545-8585, Japan.

**Abstract**

**BACKGROUND:** Currently, diagnosis of chronic fatigue syndrome (CFS) is based on clinical symptoms and therefore relies on the experience and skill of the doctors. Here, we have examined the possible diagnosis of CFS based on spectral information and chemometrics analysis, such as principal component analysis (PCA) and soft modeling of class analogy (SIMCA).

**METHODS:** Visible and near-infrared (Vis-NIR) spectroscopy was used to examine possible changes in the region of 600-1100nm in thumbs and assessed.

**RESULTS:** The Vis-NIR spectra of thumbs from 57 CFS patients and 74 healthy volunteers were subjected to PCA and SIMCA to develop multivariate models to discriminate between CFS patients and healthy individuals. The model was further assessed by the prediction of 120 determinations (60 in the healthy group and 60 in the CFS patient group). The PCA model predicted a discrimination of the masked samples; specifically the SIMCA model correctly predicted 51 of 60 (83.3%) healthy volunteers and 42 of 60 (70%) CFS patients.

**CONCLUSIONS:** Despite the relatively small numbers of subjects involved in this trial, who were exclusively Japanese, our results imply that Vis-NIR spectroscopy of the thumb combined with chemometrics analysis may provide a valuable tool for diagnosing CFS.

Pain Med. 2012 May 8. doi: 10.1111/j.1526-4637.2012.01384.x. [Epub ahead of print]

### **Home-Based Aerobic Conditioning for Management of Symptoms of Fibromyalgia: A Pilot Study.**

Harden RN, Song S, Fasen J, Saltz SL, Nampiampil D, Vo A, Revivo G., Center for Pain Studies, Rehabilitation Institute of Chicago, Chicago, Illinois Northwestern University Medical School, Chicago, Illinois Department of Behavioral Medicine, Midwestern University, Chicago, Illinois Gentiva Health Services, Bellevue, Washington Northern Colorado Medical Center, Surgical Associates of Greeley, Banner Medical Group, Greeley, Colorado Departments of Rehabilitation Medicine Anesthesiology, VA New York Harbor Healthcare System/NYU School of Medicine, New York, New York RHPH Brain and Spine Center, Rockford Health Physicians, Rockford, Illinois Center for Pain Management, Rehabilitation Institute of Chicago, Chicago, Illinois, USA.

#### **Abstract**

**Objective.** This pilot study was designed to evaluate the impact of a home-based aerobic conditioning program on symptoms of fibromyalgia and determine if changes in symptoms were related to quantitative changes in aerobic conditioning (VO<sub>2</sub> max).

**Methods.** Twenty-six sedentary individuals diagnosed with fibromyalgia syndrome participated in an individualized 12-week home-based aerobic exercise program with the goal of daily aerobic exercise of 30 minutes at 80% of estimated maximum heart rate. The aerobic conditioning took place in the participants' homes, outdoors, or at local fitness clubs at the discretion of the individual under the supervision of a physical therapist. Patients were evaluated at baseline and completion for physiological level of aerobic conditioning (VO<sub>2</sub> max), pain ratings, pain disability, depression, and stress.

**Results.** In this pilot study subjects who successfully completed the 12-week exercise program demonstrated an increase in aerobic conditioning, a trend toward decrease in pain measured by the McGill Pain Questionnaire-Short Form and a weak trend toward improvements in visual analog scale, depression, and perceived stress.

Patients who were unable or unwilling to complete this aerobic conditioning program reported significantly greater pain and perceived disability (and a trend toward more depression) at baseline than those who completed the program.

**Conclusions.** Patients suffering from fibromyalgia who can participate in an aerobic conditioning program may experience physiological and psychological benefits, perhaps with improvement in symptoms of fibromyalgia, specifically pain ratings.

More definitive trials are needed, and this pilot demonstrates the feasibility of the quantitative VO<sub>2</sub> max method. Subjects who experience significant perceived disability and negative affective symptoms are not likely to maintain a home-based conditioning program, and may need a more comprehensive interdisciplinary program offering greater psychological and social support.

Wiley Periodicals, Inc.

J Pain. 2012 May;13(5):507-15.

**Intact cognitive inhibition in patients with fibromyalgia but evidence of declined processing speed.**

Veldhuijzen DS, Sondaal SF, Oosterman JM., Pain Clinic, Division of Anesthesiology, Intensive Care and Emergency Medicine, Rudolf Magus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, The Netherlands.

**Abstract**

Patients with fibromyalgia frequently report cognitive complaints. In this study we examined performance on 2 cognitive inhibition tests, the Stroop Color-Word Test (SCWT) and the Multi-Source Interference Test (MSIT), in 35 female patients with fibromyalgia and 35 age-matched healthy female controls.

Experimental pressure pain thresholds (PPT) were determined, and fibromyalgia patients rated their current pain on a visual analog scale and completed the pain and fatigue subscales of the Fibromyalgia Impact Questionnaire. Further, all subjects completed questionnaires assessing symptoms of pain catastrophizing, depression, and anxiety.

Significant group differences were found for SCWT and MSIT performance in both the neutral (N) and interference (I) conditions with slower reaction times in patients versus controls. However, no significant group differences were found for the difference (I-N) or proportion (I/N) scores, or on the number of errors made.

For patients, pain experienced during PPT correlated significantly to several indices of cognition. Psychosocial variables were not related to cognitive test performance. Fibromyalgia patients performed worse on both tests but to a similar extent for the neutral condition and the interference condition, indicating that there is no specific problem in cognitive inhibition. Evidence of decreased mental processing and/or psychomotor speed was found in patients with fibromyalgia.

**PERSPECTIVE:** Fibromyalgia patients performed worse on interference tests, but no specific problem in cognitive inhibition was found. Decreased reaction time performance may instead point to an underlying problem of psychomotor or mental processing speed in fibromyalgia.

Future studies should examine potential deficits in psychomotor function in fibromyalgia patients in more detail.

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<http://www.ncbi.nlm.nih.gov/pubmed/22674373>

**Supervised selection of single nucleotide polymorphisms in chronic fatigue syndrome.**

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**Abstract**

**Introduction:** The different ways for selecting single nucleotide polymorphisms have been related to paradoxical conclusions about their usefulness in predicting chronic fatigue syndrome even when using the same dataset.

**Objective:** To evaluate the efficacy in predicting this syndrome by using polymorphisms selected by a supervised approach that is claimed to be a method that helps identifying their optimal profile.

**Materials and methods:** We eliminated those polymorphisms that did not meet the Hardy-Weinberg equilibrium. Next, the profile of polymorphisms was obtained through the supervised approach and three aspects were evaluated: comparison of prediction accuracy with the accuracy of a profile that was based on linkage disequilibrium, assessment of the efficacy in determining a higher risk stratum, and estimating the algorithm influence on accuracy.

**Results:** A valid profile ( $p < 0.01$ ) was obtained with a higher accuracy than the one based on linkage disequilibrium, 72.8 vs. 62.2% ( $p < 0.01$ ). This profile included two known polymorphisms associated with chronic fatigue syndrome, the NR3C1\_11159943 major allele and the 5HTT\_7911132 minor allele. Muscular pain or sinus nasal symptoms in the stratum with the profile predicted V with a higher accuracy than those symptoms in the entire dataset, 87.1 vs. 70.4% ( $p < 0.01$ ) and 92.5 vs. 71.8% ( $p < 0.01$ ) respectively. The profile led to similar accuracies with different algorithms.

**Conclusions:** The supervised approach made it possible to discover a reliable profile of polymorphisms associated with this syndrome. Using this profile, accuracy for this dataset was the highest reported and it increased when the profile was combined with clinical data.

PMID:22674373[PubMed - in process]

### **Impaired blood pressure variability in chronic fatigue syndrome—a potential biomarker**

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#### **Abstract**

**Introduction:** Autonomic dysfunction is common in chronic fatigue syndrome (CFS). This study set out to derive an autonomic biomarker using a comprehensive assessment of heart rate and blood pressure variability.

**Methods:** Heart rate and non-invasive continuous blood pressure measurements (task force monitor) at rest and on standing were performed in CFS (Fukuda n=68) and matched controls (n=68) to derive high frequency (HF; parasympathetic) and low frequency (LF; sympathetic) heart rate variability (HRV), systolic (SBPV) and diastolic (DBPV) blood pressure variability. Variables of significance were combined using receiver operator curves to explore the diagnostic utility of parameters particularly at rest.

**Results:** At rest, LF-HRV (sympathetic) was significantly increased in CFS compared to controls, while parasympathetic markers were significantly reduced (P=0.006). Total DBP spectral power was increased (P=0.0003) across all domains, with a shift towards sympathetic and away from parasympathetic SBPV (P=0.05).

On standing, overall SBPV response was significantly reduced with reductions in both sympathetic and parasympathetic components of SBPV (all P<0.0001). Change in LF-DBP and relative balance of LF/HF DBP on standing differed between CFS and controls (P<0.0001).

Using the 85% sensitivity levels, we determined a threshold for three chosen resting BPV parameters of LF DBP >3.185, rest HF DBP >0.86, rest total DBP >7.05. Achieving all of these differentiated between CFS and controls with 77% sensitivity and 53% specificity.

**Conclusion:** This study has shown that there are objectively measured abnormalities of blood pressure variability in CFS and that these abnormalities have the potential to be a bedside diagnostic tool.

Cancer. 2012 May 30. doi: 10.1002/cncr.27612.

**Chronic fatigue syndrome and subsequent risk of cancer among elderly US adults.**

Chang CM, Warren JL, Engels EA., Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland.

*Abstract*

**BACKGROUND:** The cause of chronic fatigue syndrome (CFS) is unknown but is thought to be associated with immune abnormalities or infection. Because cancer can arise from similar conditions, associations between CFS and cancer were examined in a population-based case-control study among the US elderly.

**METHODS:** Using linked Surveillance, Epidemiology, and End Results (SEER)-Medicare registry data, approximately 1.2 million cancer cases and 100,000 controls (age range, 66-99 years; 1992-2005) were evaluated. CFS was identified in the period more than 1 year prior to selection, using linked Medicare claims. Unconditional logistic regression was used to estimate the odds ratios (ORs) comparing the CFS prevalence in cases and controls, adjusting for age, sex, and selection year. All statistical tests were 2-sided.

**RESULTS:** CFS was present in 0.5% of cancer cases overall and 0.5% of controls. CFS was associated with an increased risk of non-Hodgkin lymphoma (NHL) (OR = 1.29, 95% confidence interval [CI] = 1.16-1.43,  $P = 1.7 \times 10^{-6}$ ).

Among NHL subtypes, CFS was associated with diffuse large B cell lymphoma (OR = 1.34, 95% CI = 1.12-1.61), marginal zone lymphoma (OR = 1.88, 95% CI = 1.38-2.57), and B cell NHL not otherwise specified (OR = 1.51, 95% CI = 1.03-2.23).

CFS associations with NHL overall and NHL subtypes remained elevated after excluding patients with medical conditions related to CFS or NHL, such as autoimmune conditions.

CFS was also associated, although not after multiple comparison adjustment, with cancers of the pancreas (OR = 1.25, 95% CI = 1.07-1.47), kidney (OR = 1.27, 95% CI = 1.07-1.49), breast (OR = 0.85, 95% CI = 0.74-0.98), and oral cavity and pharynx (OR = 0.70, 95% CI = 0.49-1.00).

**CONCLUSIONS:** Chronic immune activation or an infection associated with CFS may play a role in explaining the increased risk of NHL.

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'Journal of the Royal Society of Medicine Short Reports' May 2012

**Comparison of chronic fatigue syndrome/myalgic encephalopathy with other disorders: an observational study**

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**Abstract**

**OBJECTIVES:** To examine the level of activity in online discussion forums for chronic fatigue syndrome/myalgic encephalopathy (CFS/ME) compared to other disorders. We hypothesized the level of activity to be higher in CFS/ME online discussion forums.

**DESIGN:** Observational study.

**SETTING:** Norway, which has more than 80% household coverage in internet access, September 2009

**PARFTICIPANTS:** Twelve Norwegian disorder-related online discussion forums

**MAIN OUTCOME MEASURES:** Number of registered users and number of posted messages on each discussion forum.

**RESULTS:** Two forums were targeted towards individuals with CFS/ME. These forums had the highest number of registered users per estimated 1,000 cases in the population (50.5 per 1,000 and 29.7 per 1,000), followed by a site for drug dependency (5.4 per 1,000). Counting the number of posted messages per 1,000 cases gave similar indications of high online activity in the CFS/ME discussion forums.

**CONCLUSIONS:** CFS/ME online forums had more than ten times the relative activity of any other disorder or condition related forum. This high level of activity may have multiple explanations. Individuals suffering from a stigmatized condition of unknown aetiology may use the internet to look for explanations of symptoms or to seek out alternative treatments. Internet forum activity may also be reinforced by the creation of in-group identity and pre-morbid personality traits.

More knowledge on the type and quality of information provided in online forums is urgently needed.

The full version of the study can be found here: <http://bit.ly/LUXNlc>

Pain. 2012 May 20. [Epub ahead of print]

**Treatment with Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients suffering from chronic pain.**

Jensen KB, Kosek E, Wicksell R, Kemani M, Olsson G, Merle JV, Kadetoff D, Ingvar M., Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA, USA.

**Abstract**

Interventions based on Cognitive Behavioral Therapy (CBT) are widely used to treat chronic pain, but the brain mechanisms responsible for these treatment effects are poorly understood. The aim of this study was to validate the relevance of the cortical control theory in response to an exposure-based form of CBT, Acceptance and Commitment Therapy, in patients with chronic pain.

Forty-three female patients diagnosed with fibromyalgia syndrome were enrolled in a randomized, 12-week, waiting-list controlled clinical trial (CBT n=25; controls n=18). CBT was administered in groups of six patients during 12 weekly sessions.

Functional magnetic resonance imaging (fMRI) during pressure-evoked pain was assessed before and after treatment or the 12-week period. Self-report questionnaires of depression and anxiety were administered pre- and posttreatment as well as 3months following end of treatment.

Patients treated with CBT reported larger improvement of fibromyalgia on the Patient Global Impression of Change measure, and improved depression and anxiety symptoms, compared to the waiting-list controls.

However, there were no effects on clinical pain or pain sensitivity measures.

An analysis of fMRI scans revealed that CBT led to increased activations in the ventrolateral prefrontal/lateral orbitofrontal cortex; regions associated with executive cognitive control.

We suggest that CBT changes the brain's processing of pain through an altered cerebral loop between pain signals, emotions, and cognitions; leading to increased access to executive regions for reappraisal of pain. Our data thereby support our hypothesis about the activation of a cortical control mechanism in response to CBT treatment in chronic pain.

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Clin Vaccine Immunol. 2012 May 23. [Epub ahead of print]

**Evaluation of commonly used serological tests for the detection of Coxiella burnetii antibodies in well-defined acute and follow-up sera.**

Wegdam-Blans MC, Wielders CC, Meekelenkamp J, Korbeeck JM, Herremans T, Tjhie HT, Bijlmer HA, Koopmans MP, Schneeberger PM., Department of Medical Microbiology, Laboratory for Pathology and Medical Microbiology (PAMM), Veldhoven, The Netherlands.

**Abstract**

In this study we compared Coxiella burnetii IgG phase I, IgG phase II and IgM phase II detection between a commercially available Enzyme-linked Immunosorbent Assay (ELISA) (Virion/Serion), an Indirect Fluorescent Antibody Test (IFAT) (Focus Diagnostics), and a Complement Fixation Test (CFT) (Virion/Serion).

For this, we used a unique collection of acute and convalescent sera from 126 patients with acute Q fever diagnosed by positive Coxiella burnetii PCR in blood. We were able to establish a reliable date of onset of disease as DNA is detectable within two weeks after the start of symptoms.

IFAT demonstrated IgM phase II antibodies in significantly more sera compared to ELISA (32% versus 20%).

Twelve months after the diagnosis of acute Q fever, 83% and 62% of the sera were still positive for IgM phase II with IFAT and ELISA, respectively. Therefore, definitive serological evidence of acute Q fever cannot be based on a single serum sample in epidemic areas and should involve measurement of both IgM and IgG antibodies.

All tests were comparable in confirming acute Q fever using IgG phase II antibody detection in paired samples (at 0 and 3 months) from 62 patients: 100% IFAT, 95.2% ELISA and 96.8% CFT. No significant cross-reactivity to other respiratory infections was observed. IFAT demonstrated significantly more IgG phase I and IgG phase II antibodies in follow-up sera.

This study demonstrated that the three serological tests are equally effective in diagnosing acute Q fever. However, in follow-up sera, more IgG antibodies were detected by IFAT than by ELISA or CFT, making IFAT more suitable for epidemiological surveys or for pre-vaccination screening programs but not from a practical approach.

PMID: 22623653 [PubMed - as supplied by publisher]

Nihon Rinsho. 2012 May;70(5):880-6.

**Biomarkers of stress and fatigue.**

Tanaka Y., Health Research Institute, National Institute of Advanced Industrial Science and Technology (AIST).

**Abstract**

A questionnaire based survey has been commonly used for the assessment of psychological stress and stress-related diseases. Development of a quantitative approach using a non-invasive sample (i.e., saliva, hair or nails) is highly desirable to measure chronic stress.

This paper gives a brief explanation of subjective and objective (i.e., physiological signals, and biological markers) methods for stress assessment. Furthermore, it focuses particularly on the current knowledge about the biomarker candidates of chronic psychological stress and chronic fatigue syndrome (CFS).

Psychological stress is known to stimulate the autonomic nervous, endocrine, and immune systems. Since chronic stress is associated with suppression of a variety of immune parameters, some immune markers are potentially useful.

Metab Brain Dis. 2012 May 22. [Epub ahead of print]

**IgM-mediated autoimmune responses directed against anchorage epitopes are greater in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) than in major depression.**

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**Abstract**

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and depression are considered to be neuro-immune disorders (Maes and Twisk, BMC Medicine 8:35, 2010). There is also evidence that depression and ME/CFS are accompanied by oxidative and nitrosative stress (O&NS) and by increased autoantibodies to a number of self-epitopes some of which have become immunogenic due to damage by O&NS.

The aim of this study is to examine IgM-mediated autoimmune responses to different self-epitopes in ME/CFS versus depression. We examined serum IgM antibodies to three anchorage molecules (palmitic and myristic acid and S-farnesyl-L-cysteine); acetylcholine; and conjugated NO-modified adducts in 26 patients with major depression; 16 patients with ME/CFS, 15 with chronic fatigue; and 17 normal controls.

Severity of fatigue and physio-somatic (F&S) symptoms was measured with the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (<http://www.cfidsselfhelp.org/cfs-fibromyalgia-rating-scale>).

Serum IgM antibodies to the three anchorage molecules and NO-phenylalanine were significantly higher in ME/CFS than in depression.

The autoimmune responses to oxidatively, but not nitrosatively, modified self-epitopes were significantly higher in ME/CFS than in depression and were associated with F&S symptoms.

The autoimmune activity directed against conjugated acetylcholine did not differ significantly between ME/CFS and depression, but was greater in the patients than controls.

Partially overlapping pathways, i.e. increased IgM antibodies to a multitude of neo-epitopes, underpin both ME/CFS and depression, while greater autoimmune responses directed against anchorage molecules and oxidatively modified neo-epitopes discriminate patients with ME/CFS from those with depression.

These autoimmune responses directed against neoantigenic determinants may play a role in the dysregulation of key cellular functions in both disorders, e.g. intracellular signal transduction, cellular differentiation and apoptosis, but their impact may be more important in ME/CFS than in depression.

Rheumatol Int. 2012 May 12. [Epub ahead of print]

**Effect of supervised exercise program including balance exercises on the balance status and clinical signs in patients with fibromyalgia.**

Demir-Göçmen D, Altan L, Korkmaz N, Arabacı R., Department of Physical Medicine and Rehabilitation, University of Uludag, Bursa, Turkey.

**Abstract**

The objective of this study is to investigate whether the supervised exercise program including balance exercises was superior to home exercise programs in improving clinical parameters and balance status in patients with FM.

Fifty women who were diagnosed with primary FM were assigned into supervised exercise group (Group 1) and home exercise group (Group 2).

Evaluation parameters were clinical parameters [pain, number of tender points (NTP), Beck Depression Scale (BDS), Fibromyalgia Impact Questionnaire (FIQ)], and parameters associated with balance [timed up and go test (TUGT), four square step test (FSST), Berg Balance Scale (BBS), Activities-Specific Balance Confidence Scale (ABC), and static balance measurements].

Significant differences were determined between all pre- and post-exercise clinical follow-up parameters at 12th week in Group 1. There was a significant difference only in the BDS score between baseline and at the 24th week. When the changes in balance parameters in Group 1 were investigated, a significant difference was noted at the 12th week in terms of TUGT, FSST, and ABC scale scores compared to baseline; however, the significant change maintained only in ABC scale at the 24th week compared to baseline.

Significant differences were noted in all clinical parameters in Group 2 at the 12th week, whereas no difference was observed at the 24th week. Evaluation of balance parameters in Group 2 at the 12th week revealed significant differences in terms of the TUGT, FSST, BBS, and ABC scale scores compared to baseline, whereas 24th week evaluation revealed significant differences only in the BBS and ABC scale scores.

When the two groups were compared, a significant difference was observed in favor of Group 2 only for the BBS at the 12th week evaluation. Exercise programs had short-term beneficial effects on either clinical signs or dynamic balance.

PMID: 22580931 [PubMed - as supplied by publisher]

Scand J Gastroenterol. 2012 May 18. [Epub ahead of print]

**Functional bowel symptoms, fibromyalgia and fatigue: A food-induced triad?**

Berstad A, Undseth R, Lind R, Valeur J., SourceUnger-Vetlesen's Institute, Lovisenberg Diakonale Hospital.

*Abstract*

**Abstract Objective.** Patients with perceived food hypersensitivity typically present with multiple health complaints. We aimed to assess the severity of their intestinal and extra-intestinal symptoms.

**Materials and methods.** In a prospective study, 84 patients referred to our outpatient clinic for investigation of perceived food hypersensitivity were enrolled consecutively. Irritable bowel syndrome

(IBS) was diagnosed according to the Rome III criteria. Severity and impact of bowel symptoms, fatigue and musculoskeletal pain were evaluated by using the following questionnaires: The IBS Severity Scoring System (IBS-SSS), the Fatigue Impact Scale (FIS), the FibroFatigue Scale (FFS), and visual analogue scales (VAS) for scoring of musculoskeletal pain. Results. All but one patient were diagnosed with IBS, 58% with severe symptoms. Extra-intestinal symptoms suggestive of chronic fatigue and fibromyalgia were demonstrated in 85% and 71%, respectively. Neither IgE-mediated food allergy nor organic pathology could explain the patients' symptoms. Nevertheless, malabsorption of fat was demonstrated in 10 of 38 subjects.

**Conclusions.** Perceived food hypersensitivity may be associated with severe, debilitating illness. The comorbid triad of IBS, chronic fatigue, and musculoskeletal pain is striking and may point to a common underlying cause.

PMID:22594347[PubMed - as supplied by publisher]

Indian J Pharmacol. 2012 May;44(3):351-6.

**Evaluation of protective effect of Aegle marmelos Corr. in an animal model of chronic fatigue syndrome.**

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*Abstract*

**OBJECTIVE:** To evaluate ethanolic extract of leaves of Aegle marmelos in an experimental animal model of chronic fatigue syndrome for potential therapeutic benefit.

**MATERIALS AND METHODS:** Age/weight-matched female Wistar albino rats were grouped into five groups. (Group I- V) (n = 8). Group I served as naïve control and II served as stress control. Except for group I animals, other group animals were subjected to forced swimming every day for 15 minutes to induce a state of chronic fatigue and simultaneously treated with ethanolic extract of Aegle marmelos (EEAM) 150 and 250 mg/kg b.w. and Imipramine (20 mg.kg b.w.), respectively. Duration of immobility, anxiety level and locomotor activity were assessed on day 1, 7, 14 and 21 followed by biochemical estimation of oxidative biomarkers at the end of the study.

**RESULTS:** Treatment with EEAM (150 and 250 mg/kg b.w.) resulted in a statistically significant and dose dependent reduction ( $P < 0.001$ ) in the duration of immobility, reduction in anxiety and increase in locomotor activity. Dose dependent and significant reduction in LPO level and increase in CAT and SOD was observed in extract treated animals.

**CONCLUSION:** The results are suggestive of potential protective effect of A. marmelos against experimentally induced CFS.

Neurotoxicology. 2012 Jun 9. [Epub ahead of print]

**Event-related potential patterns associated with hyperarousal in gulf war illness syndrome groups.**

Tillman GD, Calley CS, Green TA, Buhl VI, Biggs MM, Spence JS, Briggs RW, Haley RW, Hart J Jr, Kraut MA.

Center for BrainHealth, The University of Texas at Dallas.

**Abstract**

An exaggerated response to emotional stimuli is one of several symptoms widely reported by veterans of the 1991 Persian Gulf War.

Many have attributed these symptoms to post-war stress; others have attributed the symptoms to deployment-related exposures and associated damage to cholinergic, dopaminergic, and white matter systems.

We collected event-related potential (ERP) data from 20 veterans meeting Haley criteria for Gulf War Syndromes 1-3 and from 8 matched Gulf War veteran controls, who were deployed but not symptomatic, while they performed an auditory three-condition oddball task with gunshot and lion roar sounds as the distractor stimuli.

Reports of hyperarousal from the ill veterans were significantly greater than those from the control veterans; different ERP profiles emerged to account for their hyperarousability.

Syndromes 2 and 3, who have previously shown brainstem abnormalities, show significantly stronger auditory P1 amplitudes, purported to indicate compromised cholinergic inhibitory gating in the reticular activating system.

Syndromes 1 and 2, who have previously shown basal ganglia dysfunction, show significantly weaker P3a response to distractor stimuli, purported to indicate dysfunction of the dopaminergic contribution to their ability to inhibit distraction by irrelevant stimuli.

All three syndrome groups showed an attenuated P3b to target stimuli, which could be secondary to both cholinergic and dopaminergic contributions or disruption of white matter integrity.

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Brain Behav Immun. 2012 Jun 8. [Epub ahead of print]

**Linking disease symptoms & subtypes with personalized systems-based phenotypes: a proof of concept study.**

Aschbacher K, Adam EK, Crofford LJ, Kemeny ME, Demitrack MA, Ben-Zvi A., Department of Psychiatry, University of California San Francisco, CA; Department of Brain, Mind & Healing, Samuelli Institute, VA.

**Abstract**

A dynamic systems model was used to generate parameters describing a phenotype of Hypothalamic-Pituitary-Adrenal (HPA) behavior in a sample of 36 patients with chronic fatigue syndrome (CFS) and/or fibromyalgia (FM) and 36 case-matched healthy controls.

Altered neuroendocrine function, particularly in relation to somatic symptoms and poor sleep quality, may contribute to the pathophysiology of these disorders.

Blood plasma was assayed for cortisol and ACTH every 10 minutes for 24 hours. The dynamic model was specified with an ordinary differential equation using three parameters: 1) ACTH-adrenal signaling, 2) inhibitory feedback, and 3) non-ACTH influences.

The model was "personalized" by estimating an individualized set of parameters from each participant's data. Day and nighttime parameters were assessed separately.

Two nocturnal parameters (ACTH-adrenal signaling and inhibitory feedback) significantly differentiated the two patient subgroups ("fatigue-predominant" patients with CFS only versus "pain-predominant" patients with FM and comorbid chronic fatigue) from controls (all  $p$ 's<.05), whereas daytime parameters and diurnal/nocturnal slopes did not.

The same nocturnal parameters were significantly associated with somatic symptoms among patients ( $p$ 's<.05).

There was a significantly different pattern of association between nocturnal non-ACTH influences and sleep quality among patients versus controls ( $p$ <.05). Although speculative, the finding that patient somatic symptoms decreased when more cortisol was produced per unit ACTH, is consistent with cortisol's anti-inflammatory and sleep-modulatory effects.

Patients' HPA systems may compensate by promoting more rapid or sustained cortisol production. Mapping "behavioral phenotypes" of stress-arousal systems onto symptom clusters may help disentangle the pathophysiology of complex disorders with frequent comorbidity.

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Zhongguo Zhong Xi Yi Jie He Za Zhi. 2012 May;32(5):599-602.

**Effects of tuina on the mechanical properties of skeletal muscles of four limbs in patients with chronic fatigue syndrome.**

[Article in Chinese]

Liu KP, Fang M, Jiang SY., Department of Tuina, Yueyang Hospital of Integrated Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437.

**Abstract**

**OBJECTIVE:** To study the effects of tuina on the mechanical properties of skeletal muscles of four limbs in patients with chronic fatigue syndrome (CFS).

**METHODS:** Thirty CFS patients were recruited as the test group, while another 30 healthy volunteers were recruited as the healthy control group. Patients in the test group received tuina therapy, 30 min each time, once every other day, for totally 10 times.

Isokinetic testing technology was used to compare peak torque (PT), total watt (TW), average power (AP), and flexor/extensor (F/E) ratio in the elbow and knee muscles of CFS patients before and after treatment. The Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale was used to evaluate the fatigue degree before and after treatment, and compared with the healthy control group.

**RESULTS:** After treatment the FACIT fatigue scale score decreased significantly in the test group when compared with before treatment (27.5 +/- 9.1 vs 42.5 +/- 11.2), showing statistical difference ( $P < 0.05$ ).

The pre-treatment PT, TW, AP, and F/E ratio in the skeletal muscle were all lower in the test group than in the healthy control group. Compared with before treatment in the test group, patients' elbow 60 degrees/s angular velocity values during exercise extensor PT and TW, knee 60 degrees/s and 180 degrees/s angular velocity values during exercise flexor PT and TW increased significantly; elbow extensor and knee extensor, flexor AP was significantly elevated; knee in 180 degrees/s angular velocity of movement F/E ratio significantly increased, and all the differences were statistically significant ( $P < 0.05$ ).

The improvement of the fatigue degree in CFS patients and elbow in 60 degrees/s angular velocity values under the flexor and extensor TW, and flexor AP value of the degree of improvement were negatively correlated ( $r = -0.282$ ,  $-0.482$ ,  $-0.285$ ,  $P < 0.05$ ,  $P < 0.01$ ).

Meanwhile, the muscles with the knee in 180 degrees/s angular velocity was negatively correlated with the F/E ratio of the degree of improvement ( $r = -0.330$ ,  $P < 0.05$ ).

**CONCLUSIONS:** CFS patients have lowered mechanical properties of four limbs. Tuina therapy can improve the biomechanical properties of limb skeletal muscle and reduce the overall degree of fatigue in patients. The changes of limb skeletal muscle and mechanical properties can provide objective reference for the clinical diagnosis and assessment of CFS.

The FACIT fatigue scale can be found here:

<http://www.integraronline.com.br/admin/download/20100222161034.pdf>

PLoS One. 2012;7(5):e37504. Epub 2012 May 25.

### **Validation of the Fibromyalgia Survey Questionnaire within a Cross-Sectional Survey.**

Häuser W, Jung E, Erbslöh-Möller B, Gesmann M, Kühn-Becker H, Petermann F, Langhorst J, Weiss T, Winkelmann A, Wolfe F., Department Internal Medicine I, Klinikum Saarbrücken, Saarbrücken, Germany.

#### **Abstract**

The Fibromyalgia Survey Questionnaire (FSQ) assesses the key symptoms of fibromyalgia syndrome. The FSQ can be administrated in survey research and settings where the use of interviews to evaluate the number of pain sites and extent of somatic symptom intensity and tender point examination would be difficult.

We validated the FSQ in a cross-sectional survey with FMS patients. In a cross-sectional survey, participants with physician diagnosis of FMS were recruited by FMS-self help organisations and nine clinical institutions of different levels of care.

Participants answered the FSQ (composed by the Widespread Pain Index [WPI] and the Somatic Severity Score [SSS]) assessing the Fibromyalgia Survey Diagnostic Criteria (FSDC) and the Patient Health Questionnaire PHQ 4. American College of Rheumatology 1990 classification criteria were assessed in a subgroup of participants.

1,651 persons diagnosed with FMS were included into analysis.

The acceptance of the FSQ-items ranged between 78.9 to 98.1% completed items. The internal consistency of the items of the SSS ranged between 0.75-0.82. 85.5% of the study participants met the FSDC. The concordance rate of the FSDC and ACR 1990 criteria was 72.7% in a subsample of 128 patients.

The Pearson correlation of the SSS with the PHQ 4 depression score was 0.52 ( $p < 0.0001$ ) and with the PHQ anxiety score was 0.51 ( $p < 0.0001$ ) (convergent validity). 64/202 (31.7%) of the participants not meeting the FSDC criteria and 152/1283 (11.8%) of the participants meeting the FSDC criteria reported an improvement (slightly too very much better) in their health status since FMS-diagnosis ( $\chi^2=55$ ,  $p < 0.0001$ ) (discriminant validity).

The study demonstrated the feasibility of the FSQ in a cross-sectional survey with FMS-patients. The reliability, convergent and discriminant validity of the FSQ were good. Further validation studies of the FSQ in clinical and general population settings are necessary.

The full study can be read here: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3360780/?tool=pubmed>

PHq 4: [www.dent.osu.edu/PCA.../PHQ-4%20handout-schiffman.pdf](http://www.dent.osu.edu/PCA.../PHQ-4%20handout-schiffman.pdf)

Clin J Pain. 2012 Jul;28(6):519-26.

**Comparing pain modulation and autonomic responses in fibromyalgia and irritable bowel syndrome patients.**

Chalaye P, Goffaux P, Bourgault P, Lafrenaye S, Devroede G, Watier A, Marchand S., Department of Surgery §Department of Medicine (Gastroenterology Service) ‡Department of Paediatrics †School of Nursing, université de Sherbrooke, Sherbrooke, Québec, Canada.

*Abstract*

**OBJECTIVES:** Past studies confirm that patients with fibromyalgia (FM) and irritable bowel syndrome (IBS) show similar pain processing dysfunctions, such as reduced pain inhibition and aberrant autonomic nervous system (ANS) responses. However, patients with FM and IBS have rarely been investigated in the same study.

The aim of the present study, therefore, was to compare descending pain inhibition, pain sensitivity, and ANS reactivity to pain in FM, IBS, and healthy controls (HC).

**METHODS:** Female patients with FM (n=10), IBS (n=13), and HCs (n=10) were exposed to multiple cold water (12°C) immersions to study pain sensitivity and descending pain inhibition. Heart rate variability was also assessed during immersions.

**RESULTS:** Pain intensity scores were highest in FM, intermediate in IBS, and smallest in HCs. In contrast, pain inhibition was absent in FM, intermediate in IBS, and strongest in HCs. Importantly, controlling for differences in pain inhibition abolished group differences in pain sensitivity. Heart rate variability analyses confirmed that, in response to mild levels of pain, patients with FM showed greater sympathetic activity whereas HCs showed greater parasympathetic activity.

Patients with IBS showed intermediate ANS responses.

**DISCUSSION:** Our results confirm the presence of graded levels of somatic hyperalgesia across patients with IBS and FM. A similar pattern of result was observed for pain inhibitory dysfunctions. These pain processing changes were accompanied by abnormal autonomic responses, which maintained patients (principally patients with FM) in a state of sympathetic hyperactivity.

Results suggest that patients with IBS and FM may present common, but graded, pain processing and autonomic dysfunctions.

PMID: 22673485 [PubMed - in process]

British Journal of Midwifery | June 2012

**Perinatal perspectives on chronic fatigue syndrome**

Yvonne Christley, Caroline J Hollins Martin, Colin R Martin British Journal of Midwifery 20(6): 389 – 393 (Jun 2012)

Chronic fatigue syndrome (CFS) is a severe, systemic, acquired illness which presents with overpowering tiredness that cannot be relieved by rest and is deteriorated through physical and mental activity. Due to the window of prevalence (20-40 years), some women diagnosed with CFS become pregnant.

Given that CFS targets women in their reproductive years, responsibility is placed upon midwives to educate, support and provide families with advice.

To equip midwives with knowledge about CFS, the objectives of this paper are to provide an overview of: how CFS impacts on reproductive health; the effects of pregnancy on CFS symptoms; CFS-related pregnancy complications; intrapartum management of women with CFS, and postpartum recovery of women with CFS.

To date, only a handful of studies have explored the relationships between CFS and childbearing, and associated complications. A greater understanding of CFS interactions with physical, psychological and social reproductive processes are required.

J Rheumatol. 2012 Jun;39(6):1125-9. Epub 2012 Apr 15.

**Rheumatic manifestations of autoimmune thyroid disease: the other autoimmune disease.**

Tagoe CE, Zezion A, Khattri S., Division of Rheumatology, Montefiore Medical Center.

**Abstract**

Autoimmune thyroid disease (AITD) is an inflammatory thyroiditis that in some cases is characterized by lymphocytic infiltration of the thyroid gland, also referred to as chronic lymphocytic thyroiditis or Hashimoto thyroiditis.

Hashimoto thyroiditis is one of the commonest causes of hypothyroidism. Hypothyroidism has been associated with osteoarthritis

(OA) and inflammatory forms of arthritis and with several well defined connective tissue diseases, which in turn can cause arthritis. The presence of arthritis in patients with AITD with normal thyroid function is now being increasingly recognized.

There is also considerable evidence to suggest that AITD is highly associated with fibromyalgia syndrome.

We review the current literature on the rheumatologic manifestations of AITD and describe the features in its presentation that set it apart from other forms of autoimmune arthritis.

Psychosomatics. 2012 Jun 5. [Epub ahead of print]

**Relationships Among Pain, Depressed Mood, and Global Status in Fibromyalgia Patients: Post Hoc Analyses of a Randomized, Placebo-Controlled Trial of Milnacipran.**

Arnold LM, Palmer RH, Gendreau RM, Chen W., Women's Health Research Program, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH.

*Abstract*

**BACKGROUND:** Patients with fibromyalgia often experience depressive symptoms in addition to chronic pain and other characteristic symptoms associated with this disorder.

**OBJECTIVE:** To examine the relationships among pain, depressive symptoms, and global status in a clinical trial of milnacipran for fibromyalgia.

**METHODS:** Data from a randomized, double-blind study (milnacipran 100 mg/d, n = 516; placebo, n = 509) were analyzed. Treatment outcomes included quantitative changes in pain and Beck Depression Inventory (BDI) scores, mean Patient Global Impression of Change (PGIC) scores, and three responder endpoints: patients with  $\geq 30\%$  pain improvement, PGIC score  $\leq 2$ , and patients meeting both pain and PGIC responder criteria (2-measure composite responders). Correlations and path analyses were conducted to evaluate relationships among improvements in depressive symptoms, pain, and PGIC.

**RESULTS:** Patients receiving milnacipran had greater decreases in mean pain scores, lower mean PGIC endpoint scores, and higher responder rates regardless of baseline severity of depressive symptoms. The highest responder rates were found in patients with greater than four-point improvement in BDI scores (milnacipran vs. placebo: pain, 57.5% vs. 39.0%; PGIC, 60.1% vs. 38.2%; 2-measure composite, 49.0% vs. 27.9%; all  $p < 0.01$ ), although significant differences between treatment groups were also found in patients with no improvement or worsening of depressive symptoms.

Correlations between changes in BDI and changes in pain or PGIC were low ( $r \leq 0.3$ ). Path analyses indicated 87.2% of pain reduction to be a direct effect of milnacipran treatment.

**Conclusion:** Symptom improvements with milnacipran were only weakly associated with baseline depressive symptoms and were largely independent of improvements in depressive symptomatology.

### **Impaired blood pressure variability in chronic fatigue syndrome—a potential biomarker**

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Received April 4, 2012. Revision received April 13, 2012.

#### **Abstract**

**Introduction:** Autonomic dysfunction is common in chronic fatigue syndrome (CFS). This study set out to derive an autonomic biomarker using a comprehensive assessment of heart rate and blood pressure variability.

**Methods:** Heart rate and non-invasive continuous blood pressure measurements (task force monitor) at rest and on standing were performed in CFS (Fukuda n=68) and matched controls (n=68) to derive high frequency (HF; parasympathetic) and low frequency (LF; sympathetic) heart rate variability (HRV), systolic (SBPV) and diastolic (DBPV) blood pressure variability. Variables of significance were combined using receiver operator curves to explore the diagnostic utility of parameters particularly at rest.

**Results:** At rest, LF-HRV (sympathetic) was significantly increased in CFS compared to controls, while parasympathetic markers were significantly reduced (P=0.006). Total DBP spectral power was increased (P=0.0003) across all domains, with a shift towards sympathetic and away from parasympathetic SBPV (P=0.05).

On standing, overall SBPV response was significantly reduced with reductions in both sympathetic and parasympathetic components of SBPV (all P<0.0001). Change in LF-DBP and relative balance of LF/HF DBP on standing differed between CFS and controls (P<0.0001).

Using the 85% sensitivity levels, we determined a threshold for three chosen resting BPV parameters of LF DBP >3.185, rest HF DBP >0.86, rest total DBP >7.05. Achieving all of these differentiated between CFS and controls with 77% sensitivity and 53% specificity.

**Conclusion:** This study has shown that there are objectively measured abnormalities of blood pressure variability in CFS and that these abnormalities have the potential to be a bedside diagnostic tool.

Nutr Hosp. 2012 Apr;27(2):659-62.

**Patterns of food avoidance in chronic fatigue syndrome: is there a case for dietary recommendations?**

Trabal J, Leyes P, Fernández-Solá J, Forga M, Fernández-Huerta J., Servei d'Endocrinologia i Nutrició, Hospital Clínic, Barcelona, Spain.

*Abstract*

**Objectives:** To assess the dietary habits and food avoidance-behavior in patients with Chronic Fatigue Syndrome (CFS).

**Methods:** Cross-sectional pilot study with 28 patients diagnosed with severe CFS. Eating habits were assessed with a food frequency questionnaire and 3-day food records. We analyzed variables related to dietary restrictions induced by symptoms or external information.

**Results:** The most prevalent restrictions were for dairy products and gluten-containing grains, with 22 and 15 restricting patients, respectively. Patients reported different digestive symptoms, which did not improve with the use of exclusion diets.

Thirteen patients had received information against the intake of certain foods through different sources. Six cases of grains restriction and 11 of dairy were compatible with a counseling-induced pattern of exclusion.

**Conclusions:** There is not a homogeneous pattern of food avoidance. Dietary restrictions should be based on a proven food allergy or intolerance. Dietary counseling should be based on sound nutritional knowledge.

PMID: 22732998 [PubMed - in process]

Brain Behav Immun. 2012 Jun 22. [Epub ahead of print]

### **Biomarkers for Chronic Fatigue.**

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#### **Abstract**

Fatigue that persists for 6 months or more is termed chronic fatigue. Chronic fatigue (CF) in combination with a minimum of 4 of 8 symptoms and the absence of diseases that could explain these symptoms, constitute the case definition for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME).

Inflammation, immune system activation, autonomic dysfunction, impaired functioning in the hypothalamic-pituitary-adrenal axis, and neuroendocrine dysregulation have all been suggested as root causes of fatigue.

The identification of objective markers consistently associated with CFS/ME is an important goal in relation to diagnosis and treatment, as the current case definitions are based entirely on physical signs and symptoms.

This review is focused on the recent literature related to biomarkers for fatigue associated with CFS/ME and, for comparison, those associated with other diseases. These markers are distributed across several of the body's core regulatory systems.

A complex construct of symptoms emerges from alterations and/or dysfunctions in the nervous, endocrine and immune systems. We propose that new insight will depend on our ability to develop and deploy an integrative profiling of CFS/ME pathogenesis at the molecular level.

Until such a molecular signature is obtained efforts to develop effective treatments will continue to be severely limited.

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Med Hypotheses. 2012 Jun;78(6):752-6. Epub 2012 Mar 23.

**Biological underpinnings of the commonalities in depression, somatization, and Chronic Fatigue Syndrome.**

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*Abstract*

**BACKGROUND:** Somatization is a multisomatoform disorder characterized by medically unexplained, functional or psychosomatic symptoms. Similar somatic symptoms are key components of depression and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

**METHODS:** This paper reviews the evidence that such symptoms are organically based. We use the term "physio-somatic" to describe these symptoms.

**RESULTS:** Inflammation, cell-mediated immune (CMI) activation and alterations in the tryptophan catabolite (TRYCAT) pathway are associated with the physio-somatic symptoms of depression, ME/CFS and/or somatization.

Proinflammatory cytokines, decreased tryptophan and aberrations in TRYCATs may cause physio-somatic symptoms, such as fatigue, autonomic symptoms, hyperalgesia and somatic presentations.

**CONCLUSIONS:** The data suggest co-ordinated and interacting biological pathways driving the occurrence of physio-somatic symptoms across these three disorders, giving a biologically validated "pathway phenotype".

These data have far-reaching implications for DSM-IV diagnostic conceptualizations of somatization (and ME/CFS) suggesting the presence of an emerging organic explanation.

Future research should focus on the role of immune regulation, and co-ordination, of neuronal activity and, through larger data sets, ultimately creating new, biologically validated classification rules.

These data have implications for the development of novel therapies utilizing these insights, buttressing the role of psychotherapy in psychosomatic presentations.

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Experimental Biology and Medicine

### **Hematologic and Urinary Excretion Anomalies in Patients with Chronic Fatigue Syndrome**

Suzanne H. Niblett et al, \*Environmental and Pathogenic Microbiology Laboratory, Discipline of Biological Sciences, University of Newcastle, Callaghan 2308, Australia; et al.

#### **Abstract**

This report outlines the results of a single-blind, cross-sectional research project that extensively investigated a large cohort of 100 CFS patients and 82 nonfatigued control subjects.

The case-control comparison of the blood cell data revealed that CFS patients had a significant decrease in red cell distribution width and increases in mean platelet volume, neutrophil counts, and the neutrophil-lymphocyte ratio.

Evaluation of the urine excretion parameters also revealed a number of anomalies. The overnight urine output and rate of amino acid excretion were both reduced in the CFS group ( $P < 0.01$ ). Significant decreases in the urinary excretion of asparagine ( $P < 0.0001$ ), phenylalanine ( $P < 0.003$ ), the branch chain amino acids ( $P < 0.005$ ), and succinic acid ( $P < 0.0001$ ), as well as increases in 3-methylhistidine ( $P < 0.05$ ) and tyrosine ( $P < 0.05$ ) were observed.

It was concluded that the urinary excretion and blood parameters data supported the hypothesis that alterations in physiologic homeostasis exist in CFS patients.

**Introduction:** Several studies have suggested that disturbances in amino acid homeostasis occur in CFS (13–18) and other clinically overlapping syndromes (19–22).

In a recent study, CFS subjects were shown to have significant reductions in the urinary excretion of beta-alanine, hydroxyproline, histidine, methionine, cystine, and phenylalanine compared with nonfatigued controls (18).

Importantly, this report also showed that the excretion profiles of CFS patients were different from patients with depression and rheumatoid arthritis, suggesting that the urinary excretion in CFS patients reflects different metabolic perturbations compared with other patient groups.

Significant reductions in plasma taurine, histidine, alpha-aminobutyric acid, and tyrosine were also noted for the CFS group. It was concluded that the results were consistent with inflammatory disease and warranted further investigation. However, the patient size used in this research project was small (30 subjects), and therefore caution should be applied in attempting to generalize these findings to all CFS patients.

The aim of this investigation was to assess urine metabolite excretion and blood cell parameters from 100 CFS patients who have been compared with 82 control subjects to test the hypothesis that CFS patients have a molecular and cellular basis to the disorder.

**Conclusions.** The results of this study revealed that patients with CFS/ME had anomalies in blood parameters, urine excretion volume, and urinary excretion of amino acids compared with age- and sex-matched nonfatigued controls.

Reductions in overnight urinary output and a generalized depletion in the rate of amino acid excretion, in particular, depletions in the excretion of branched chain amino acids, were the most prominent alterations observed.

These findings indicated significant disturbance to amino acid and nitrogen metabolism and homeostasis. Further investigation into the mechanisms underlying these changes and their etiologic and clinical significance is warranted.

Am J Phys Med Rehabil. 2012 Jul;91(7):574-83.

**Association between body mass index and response to a brief interdisciplinary treatment program in fibromyalgia.**

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*Abstract*

**OBJECTIVE:** The aim of this study was to evaluate the association between baseline body mass index (BMI) and treatment outcome after a brief interdisciplinary fibromyalgia treatment program.

**DESIGN:** Subjects (n = 477) with fibromyalgia participated in the fibromyalgia treatment program. They completed the Fibromyalgia Impact Questionnaire (FIQ) and the Short Form-36 Health Status Questionnaire (SF-36) at baseline and 6 to 12 mos after the fibromyalgia treatment program. Posttreatment changes in FIQ and SF-36 scores were compared after stratifying participants into four BMI groups: nonobese, overweight, moderately obese, and severely obese.

**RESULTS:** All BMI groups achieved significant improvement in the FIQ total score; the FIQ subscales feel good, pain, fatigue, and morning tiredness; and the SF-36 subscales pain index, vitality, social functioning, and mental health index. Posttreatment changes in mean scores for each subscale generally did not differ significantly across BMI groups after adjusting for age and baseline scores. However, the

SF-36 subscale scores of physical functioning and role-emotional were significantly less improved in the severely obese compared with the nonobese.

**CONCLUSIONS:** Baseline BMI did not affect response to the fibromyalgia treatment program, as measured by the FIQ total score or SF-36 physical and mental component summary scores. However, the severely obese group showed less improvement compared with the nonobese group in the SF-36 physical functioning and role-emotional subscales.

Expert Opin Pharmacother. 2012 Jun 20. [Epub ahead of print]

**Off-label uses of trazodone: a review.**

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**Abstract**

**Introduction:** Trazodone is an antidepressant belonging to the class of serotonin receptor antagonists and reuptake inhibitors. It is approved by the FDA for the treatment of depression. Insomnia is the most frequent reason for prescription of trazodone. It has also been proven useful in the treatment of anxiety disorders.

Other off-label uses include the treatment of bulimia, benzodiazepine/alcohol dependence, fibromyalgia, central nervous system degenerative diseases (behavioral disorders in dementia and other organic disorders), schizophrenia, chronic pain disease and diabetic neuropathy, sexual dysfunction.

**Areas covered:** This paper evaluates trazodone's efficacy and safety in its off-label uses. It also discusses the possibility that a combination of trazodone with SSRIs may prevent or treat some of the SSRI side effects, such as anxiety, insomnia and sexual dysfunction, in addition to synergically increasing SSRIs' antidepressant activity.

**Expert opinion:** Few clinical trials have been conducted to evaluate trazodone's efficacy in the treatment of the diseases and symptoms for which it is often used in clinical practice. More studies are necessary to investigate possible new therapeutic indications, and to scientifically demonstrate the risk/benefit ratio for the many conditions for which trazodone is used, but not approved by the FDA.

PMID: 22712761 [PubMed - as supplied by publisher]

PLoS One. 2012;7(6):e37808. Epub 2012 Jun 8.

**Working memory impairment in fibromyalgia patients associated with altered frontoparietal memory network.**

Seo J, Kim SH, Kim YT, Song HJ, Lee JJ, Kim SH, Han SW, Nam EJ, Kim SK, Lee HJ, Lee SJ, Chang Y., Department of Medical and Biological Engineering, Kyungpook National University, Dong-In dong, Jung-gu, Daegu, Korea.

**Abstract**

**BACKGROUND:** The objective of this study was to investigate the differences in neural correlates of working memory between FM patients and healthy subjects, using functional magnetic resonance imaging (MRI).

**METHODOLOGY/PRINCIPAL FINDINGS:** Nineteen FM patients and 22 healthy subjects performed an n-back memory task during MRI scan. Functional MRI data were analyzed using within- and between-group analysis. Both activated and deactivated brain regions during n-back task were evaluated. In addition, to investigate the possible effect of depression and anxiety, group analysis was also performed with depression and anxiety level in terms of Beck depression inventory (BDI) and Beck anxiety inventory (BAI) as a covariate.

Between-group analyses, after controlling for depression and anxiety level, revealed that within the working memory network, inferior parietal cortex was strongly associated with the mild ( $r=0.309$ ,  $P=0.049$ ) and moderate ( $r=0.331$ ,  $P=0.034$ ) pain ratings. In addition, between-group comparison revealed that within the working memory network, the left DLPFC, right VLPFC, and right inferior parietal cortex were associated with the rating of depression and anxiety?

**Discussion in part:** "our data revealed that within frontoparietal working memory network, inferior parietal cortex showed significantly lower activation in the FM group than in the control group even after controlling for depression and anxiety. Furthermore, the neural activity in the inferior parietal cortex showed close correlation with pain threshold in each subjects. Therefore, the impairment in the inferior parietal cortex of the frontoparietal working memory network was associated not only with depression and anxiety but also with pain itself. Previous studies showed functional impairments in the inferior parietal cortex in FM patients.

**CONCLUSIONS/SIGNIFICANCE:** Our results suggest that the working memory deficit found in FM patients may be attributable to differences in neural activation of the frontoparietal memory network and may result from both pain itself and depression and anxiety associated with pain.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3370998/?tool=pubmed>

Curr Pain Headache Rep. 2012 Jun 21. [Epub ahead of print]

### **Brain Imaging in Fibromyalgia.**

Jorge LL, Amaro E Jr., Hospital Israelita Albert Einstein and Instituto de Reabilitação "Lucy Montoro", Avenida Albert Einstein, 627 3rd Floor Block D, 05651901, Morumbi, Sao Paulo, Brazil.

#### **Abstract**

Fibromyalgia is a primary brain disorder or a result of peripheral dysfunctions inducing brain alterations, with underlying mechanisms that partially overlap with other painful conditions.

Although there are methodologic variations, neuroimaging studies propose neural correlations to clinical findings of abnormal pain modulation in fibromyalgia.

Growing evidences of specific differences of brain activations in resting states and pain-evoked conditions confirm clinical hyperalgesia and impaired inhibitory descending systems, and also demonstrate cognitive-affective influences on painful experiences, leading to augmented pain-processing.

Functional data of neural activation abnormalities parallel structural findings of gray matter atrophy, alterations of intrinsic connectivity networks, and variations in metabolites levels along multiple pathways.

Data from positron-emission tomography, single-photon-emission-computed tomography, blood-oxygen-level-dependent, voxel-based morphometry, diffusion tensor imaging, default mode network analysis, and spectroscopy enable the understanding of fibromyalgia pathophysiology, and favor the future establishment of more tailored treatments.

PMID: 22717698 [PubMed - as supplied by publisher]

Clinica Chimica Acta In Press, Accepted Manuscript — Note to users

### **NMR metabolic profiling of serum identifies amino acid disturbances in Chronic Fatigue Syndrome**

Christopher W. Armstrong<sup>a, b</sup>, Neil R. McGregor<sup>c</sup>, John R. Sheedy<sup>d</sup>, Ian Buttfelde, Henry L. Buttb, f, Paul R. Gooleya, b.

**Abstract** Chronic fatigue syndrome (CFS) is a debilitating multisystem disorder characterized by long-term fatigue with a variety of other symptoms including cognitive dysfunction, unrefreshing sleep, muscle pain, and post-exertional malaise. It is a poorly understood condition that occurs in ~ 5 in every 1000 individuals.

We present here a preliminary study on the analysis of blood samples from 11 CFS and 10 control subjects through NMR metabolic profiling.

Identified metabolites that were found to be significantly altered between the groups were subjected to correlation analysis to potentially elucidate disturbed metabolic pathways.

Our results showed a significant reduction of glutamine ( $P = 0.002$ ) and ornithine ( $P < 0.05$ ) in the blood of CFS samples. Correlation analysis of glutamine and ornithine with other metabolites in the CFS sera showed relationships with glucogenic amino acids and metabolites that participate in the urea cycle. This indicates a possible disturbance to amino acid and nitrogen metabolism.

It would be beneficial to identify any potential biomarkers of CFS for accurate diagnosis of the disorder.

**Highlights:** ► <sup>1</sup>H NMR was used for metabolic profiling serum of chronic fatigue syndrome patients. ► Reductions in glutamine and ornithine levels were observed. ► Data indicates a possible disturbance to amino acid and nitrogen metabolism.

Metab Brain Dis. 2012 Jun 21. [Epub ahead of print]

**A neuro-immune model of Myalgic Encephalomyelitis/Chronic fatigue syndrome.**

Morris G, Maes M., Source Tir Na Nog, Pembrey, Llanelli, UK.

**Abstract**

This paper proposes a neuro-immune model for Myalgic Encephalomyelitis/Chronic fatigue syndrome (ME/CFS). A wide range of immunological and neurological abnormalities have been reported in people suffering from ME/CFS. They include abnormalities in proinflammatory cytokines, raised production of nuclear factor- $\kappa$ B, mitochondrial dysfunctions, autoimmune responses, autonomic disturbances and brain pathology. Raised levels of oxidative and nitrosative stress (O&NS), together with reduced levels of antioxidants are indicative of an immuno-inflammatory pathology. A number of different pathogens have been reported either as triggering or maintaining factors. Our model proposes that initial infection and immune activation caused by a number of possible pathogens leads to a state of chronic peripheral immune activation driven by activated O&NS pathways that lead to progressive damage of self epitopes even when the initial infection has been cleared. Subsequent activation of autoreactive T cells conspiring with O&NS pathways cause further damage and provoke chronic activation of immuno-inflammatory pathways.

The subsequent upregulation of proinflammatory compounds may activate microglia via the vagus nerve. Elevated proinflammatory cytokines together with raised O&NS conspire to produce mitochondrial damage.

The subsequent ATP deficit together with inflammation and O&NS are responsible for the landmark symptoms of ME/CFS, including post-exertional malaise. Raised levels of O&NS subsequently cause progressive elevation of autoimmune activity facilitated by molecular mimicry, bystander activation or epitope spreading. These processes provoke central nervous system (CNS) activation in an attempt to restore immune homeostasis. This model proposes that the antagonistic activities of the CNS response to peripheral inflammation, O&NS and chronic immune activation are responsible for the remitting-relapsing nature of ME/CFS. Leads for future research are suggested based on this neuro-immune model.

PMID:22718491[PubMed - as supplied by publisher]

Child Care Health Dev. 2012 Jun 19. doi:

10.1111/j.1365-2214.2012.01397.x. [Epub ahead of print]

**Self-esteem of children and adolescents with chronic illness: a meta-analysis.**

Pinquart M., Department of Psychology, Philipps University, Marburg, Germany.

**Abstract**

Chronic illness may be a risk factor for low self-esteem; however, previous meta-analyses are inconclusive whether children with a chronic illness have lower self-esteem than their healthy peers. The goal of the present study was to summarize available research in order to compare the self-esteem of children and adolescents with a chronic illness with that of healthy children.

Random-effects meta-analysis was used to integrate the results of 621 empirical studies that compare levels of self-esteem of children with a chronic physical illness with healthy peers or general test norms.

Studies were identified via the electronic databases Adolesc, Embase, Google Scholar, MEDLINE, PSYDEX, PSYCINFO, and cross-referencing.

Children with chronic illnesses have lower self-esteem than healthy peers or test norms ( $g=-0.18$  standard deviation units). The lowest levels of self-esteem were observed in children with chronic fatigue syndrome and chronic headaches.

Lower levels of self-esteem in children with a chronic illness were found in girls than in boys, in adolescents than in children, in children from developing or threshold countries, when results were collected from observer ratings rather than child reports, in studies published in the 1990s, and when children with chronic illnesses were directly compared with healthy children instead of test norms.

Paediatricians, parents, and teachers should promote experiences of success and positive peer-relations, which are important sources of self-esteem. In addition, psychosocial interventions for children with chronic illnesses should be offered for children with reduced self-esteem.

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NeuroUrol Urodyn. 2012 Jun 5. doi: 10.1002/nau.22277. [Epub ahead of print]

**The association between overactive bladder and fibromyalgia syndrome: A community survey.**

Chung JH, Kim SA, Choi BY, Lee HS, Lee SW, Kim YT, Lee TY, Moon HS., Department of Urology, Hanyang University College of Medicine, Seoul, Korea.

*Abstract*

**AIMS:** Fibromyalgia syndrome (FMS) is the most common disease causing chronic generalized pain, and FMS patients often complain of urinary symptoms such as frequency or urgency. This study focuses on the association of overactive bladder (OAB) and FMS in adults aged 40 and over.

**METHODS:** A survey of adults aged 40s and over was conducted in the Guri and Yangpyeong areas of South Korea. The response rate was 74.2% (940/1,266). After excluding subjects with incomplete questionnaires (n = 20), 920 were included in the final analysis. The association of FMS and OAB was analyzed by univariate and multivariate logistic regression analysis.

**RESULTS:** Individuals with FMS had a significantly increased symptoms of OAB after adjustment for gender, age group, and area of residence (odds ratio (OR) 3.39, 95% confidence interval (CI) 1.82-6.31). The association between FMS and severity of OAB was statistical significant (P for trend <0.0001).

**CONCLUSIONS:** OAB is associated with FMS. Moreover FMS increases with severity of OAB. NeuroUrol. Urodynam. © 2012 Wiley Periodicals, Inc.

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PMID: 22674758 [PubMed - as supplied by publisher]

Clin J Pain. 2012 Jun 7. [Epub ahead of print]

**Long-term Maintenance of Response Across Multiple Fibromyalgia Symptom Domains in a Randomized Withdrawal Study of Pregabalin.**

Pauer L, Atkinson G, Murphy TK, Petersel D, Zeiher B., \*Pfizer Global Research and Development, New London, CT †Pfizer Global Research and Development, Sandwich, Kent, UK ‡Pfizer Inc., New York, NY.

*Abstract*

**OBJECTIVE:** To determine the incidence and duration of response of clinically meaningful improvements with pregabalin across several key symptoms of fibromyalgia (FM).

**METHODS:** This was a post hoc analysis of data from a multicenter, double-blind, placebo-controlled, randomized, withdrawal study, originally designed to evaluate the efficacy of pregabalin monotherapy for durability of effect on FM pain based on pain and Patient Global Impression of Change (PGIC) criteria.

Responder criteria for Fibromyalgia Impact Questionnaire total score ( $\geq 16$ -point change), Medical Outcomes Study Sleep Scale Sleep Disturbance subscale ( $\geq 15.8$ -point change), and the 36-item Short-Form Health Survey Vitality scale [Measures energy and fatigue] ( $\geq 10$ -point

change) were used to evaluate the incidence and duration of improvements in function, sleep, and fatigue for pregabalin versus placebo among pain and PGIC responders.

A composite responder index consisting of pain, PGIC, function, and sleep endpoints was used to explore multidimensional response.

**RESULTS:** Approximately 80% of patients meeting pain and PGIC improvement criteria at randomization had clinically meaningful improvement in fatigue, sleep, or function.

Higher proportions of patients in the pregabalin group maintained a clinically meaningful response, and pregabalin-treated patients had a significantly longer time to loss of therapeutic response compared with the placebo group.

Composite responder Kaplan-Meier analysis, performed with patients demonstrating clinically meaningful improvements in pain, PGIC, function, and sleep at randomization showed a significantly longer median time to loss of therapeutic response for pregabalin-treated patients.

**DISCUSSION:** The results from this post hoc analysis indicate that pregabalin provides long-term effects across multiple domains of FM.

(ClinicalTrials.gov registry ID: NCT00151489).

Pain Res Treat. 2012;2012:938595. Epub 2012 Jun 3.

**Temporal summation of pain is not amplified in a large proportion of fibromyalgia patients.**

Potvin S, Paul-Savoie E, Morin M, Bourgault P, Marchand S., Centre de Recherche Fernand-Seguin and Department of Psychiatry, Faculty of Medicine, Université de Montréal, QC, Canada H1N 3V2.

**Abstract**

**Background.** Recently, it has been proposed that fibromyalgia (FM), a chronic widespread pain syndrome, results from overactive endogenous excitatory pain mechanisms. Experimental studies using temporal summation paradigms have confirmed this hypothesis but have included small samples of patients, prompting our group to perform a large-scale study.

**Methods.** Seventy-two female FM patients and 39 healthy females participated in the study. The temporal summation test consisted of a 2-minute continuous and constant heat pulse administered with a thermode on the participants' left forearm. Experimental temperature was set at a value individually predetermined to induce a 50/100 pain rating.

**Results.** Relative to controls, FM patients had lower thermal pain thresholds and lower temporal summation of pain. However, 37 FM patients required experimental temperatures lower than the minimal temperature used in controls (45°C).

Nevertheless, temporal summation was not increased in the other FM subgroup, relative to controls, despite equivalent experimental temperatures.

**Discussion.** Our results suggest that temporal summation of pain is normal, rather than increased, in a large proportion of FM patients.

Future studies on temporal summation in FM will need to be careful since some FM patients require abnormally low experimental temperatures that may confound results and make necessary to separate patients into subgroups.

Full study here: <http://www.hindawi.com/journals/prt/2012/938595/>

## ***Patients With Fibromyalgia Display Less Functional Connectivity In The Brain's Pain Inhibitory Network***

**Karin B Jensen, Rita Loitole, Eva Kosek, Frank Petzke, Serena Carville, peter Fransson, Hanke Marcus, Steven C.R Williams, Ernest Choy, Yves Mainguy, Olivier Vitton, Richard H Gracely, Randy Gollub, Martin Ingvar and Jian Kong**

***Molecular Pain*** 2012, **8**:32 doi:10.1186/1744-8069-8-32

Published: 26 April 2012

### ***Abstract (provisional)***

#### ***Background***

There is evidence for augmented processing of pain and impaired endogenous pain inhibition in Fibromyalgia syndrome (FM). In order to fully understand the mechanisms involved in FM pathology, there is a need for closer investigation of endogenous pain modulation. In the present study, we compared the functional connectivity of the descending pain inhibitory network in age-matched FM patients and healthy controls (HC). We performed functional magnetic resonance imaging (fMRI) in 42 subjects; 14 healthy and 28 age-matched FM patients (2 patients per HC), during randomly presented, subjectively calibrated pressure pain stimuli. A seed-based functional connectivity analysis of brain activity was performed. The seed coordinates were based on the findings from our previous study, comparing the fMRI signal during calibrated pressure pain in FM and HC: the rostral anterior cingulate cortex (rACC) and thalamus.

#### ***Results***

FM patients required significantly less pressure (kPa) to reach calibrated pain at 50 mm on a 0-100 visual analogue scale ( $p < .001$ , two-tailed). During fMRI scanning, the rACC displayed significantly higher connectivity to the amygdala, hippocampus, and brainstem in healthy controls, compared to FM patients. There were no regions where FM patients showed higher rACC connectivity. Thalamus showed significantly higher connectivity to the orbitofrontal cortex in healthy controls but no regions showed higher thalamic connectivity in FM patients.

#### ***Conclusion***

Patients with FM displayed less connectivity within the brain's pain inhibitory network during calibrated pressure pain, compared to healthy controls. The present study provides brain-imaging evidence on how brain regions involved in homeostatic control of pain are less connected in FM patients. It is possible that the dysfunction of the descending pain modulatory network plays an important role in maintenance of FM pain and our results may translate into clinical implications by using the functional connectivity of the pain modulatory network as an objective measure of pain dysregulation.

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[www.ijcem.com](http://www.ijcem.com) /ISSN:1940-5901/IJCEM1204005

## Original Article

# Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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**Abstract:** The objectives of this study are to test the hypothesis that the fatigue and accompanying symptoms of Chronic Myalgic Encephalomyelitis/Fatigue Syndrome are in part due to defects in energy provision at the cellular level, and to understand the pathophysiology of the defects so that effective medical intervention can be implemented. We performed an audit of 138 patients (ages 18-65) diagnosed with ME/CFS and attending a private practice. The patients and 53 normal, healthy controls had the ATP Profile test carried out on neutrophils from a 3-ml venous blood sample. This test yields 6 numerical factors that describe the availability of ATP and the efficiency of oxidative phosphorylation in mitochondria. Other biomedical measurements, including the concentration of cell-free DNA in plasma, were made. The results of the audit are compared with the controls and a previous cohort of 61 patients. We find that all patients tested have measureable mitochondrial dysfunction which correlates with the severity of the illness. The patients divide into two main groups differentiated by how cellular metabolism attempts to compensate for the dysfunction. Comparisons with exercise studies suggest that the dysfunction in neutrophils also occurs in other cells. This is confirmed by the cell-free DNA measurements which indicate levels of tissue damage up to 3.5 times the normal reference range. The major immediate causes of the dysfunction are lack of essential substrates and partial blocking of the translocator protein sites in mitochondria. The ATP Profile is a valuable diagnostic tool for the clinical management of ME/CFS.

**Keywords:** Chronic fatigue syndrome, myalgic encephalomyelitis, mitochondria, adenosine triphosphate (ATP), oxidative phosphorylation, cellular energetic, glycolysis, cell-free DNA, exercise

## ***Understanding Long-Term Outcomes of Chronic Fatigue Syndrome***

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Article first published online: 29 JUN 2012

### ***Journal of Clinical Psychology***

Brown, M. M., Bell, D. S., Jason, L. A., Christos, C. and Bell, D. E. (2012), Understanding Long-Term Outcomes of Chronic Fatigue Syndrome. *J. Clin. Psychol.* doi: 10.1002/jclp.21880

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Article first published online: 29 JUN 2012

## **Objective**

This study sought to examine long-term health, symptom, and disability outcomes among patients with chronic fatigue syndrome (CFS) by comparing those diagnosed with CFS 25 years ago with healthy controls.

## **Method**

Of the 25 participants diagnosed with CFS 25 years ago, 5 self-reported that they maintained a diagnosis of CFS, while 20 reported no longer having a diagnosis. These two groups were compared with healthy controls on outcomes related to functioning and symptom severity.

## **Results**

Those who remitted from CFS showed significantly more impairment on 21 out of 23 outcomes compared with controls. On 17 outcomes, those who remitted had nonsignificant differences in impairment compared to those who maintained a CFS diagnosis.

Tijdschr Psychiatr. 2012;54(6):517-26.

**Neuro-endocrine correlates of burnout.**

[Article in Dutch]

Verhaeghe J, Van Den Eede F, Van Den Aemele H, Sabbe BG.

**Abstract**

The symptoms of burnout are similar to those of depression on the one hand and chronic fatigue syndrome on the other hand. However, the neuro-endocrine correlates of these two syndromes are the opposite, the former being a hyperfunction of the hypothalamic-hypophysial-cortical axis and the latter being a hypofunction of the hpa-axis.

To find out, via a systematic review of the literature, whether burnout is associated with either a hyperfunction or a hypofunction of the hpa-axis. We searched PubMed using the following search terms:

burnout syndrome and burnout, adrenocorticotrophic hormone;corticotropin releasing factor; hypothalamic pituitary adrenal axis; and cortisol. We retrieved 16 original articles and one meta-analysis were included in the study.

Functional stress testing showed hypersuppression of the hpa-axis after dexamethasone. Basal cortisol values were found to be less conclusive, although a meta-analysis pointed to a negative association between burnout and cortisol. We did not find any studies that were carried out with the help of physiological, physical or psychological stress factors in burnout.

**Conclusion:** Burnout is associated primarily with a hypofunction of the hpa-axis, which is a neuro-endocrine characteristic of exhaustion, rather than of depression. However, further studies involving functional stress testing are needed in order to map the neuro-endocrine profile fully and to clarify the link with the deregulation of the immune system.

PMID: 22753184 [PubMed - in process]

Best translation found: <http://translate.google.com/translate?hl=en&sl=nl&tl=en&...>

Nutr Hosp. 2012 Apr;27(2):659-62.

**Patterns of food avoidance in chronic fatigue syndrome: is there a case for dietary recommendations?**

Trabal J, Leyes P, Fernández-Solá J, Forga M, Fernández-Huerta J., Servei d'Endocrinologia i Nutrició, Hospital Clínic, Barcelona, Spain.

*Abstract*

**Objectives:** To assess the dietary habits and food avoidance-behavior in patients with Chronic Fatigue Syndrome (CFS).

**Methods:** Cross-sectional pilot study with 28 patients diagnosed with severe CFS. Eating habits were assessed with a food frequency questionnaire and 3-day food records. We analyzed variables related to dietary restrictions induced by symptoms or external information.

**Results:** The most prevalent restrictions were for dairy products and gluten-containing grains, with 22 and 15 restricting patients, respectively. Patients reported different digestive symptoms, which did not improve with the use of exclusion diets.

Thirteen patients had received information against the intake of certain foods through different sources. Six cases of grains restriction and 11 of dairy were compatible with a counseling-induced pattern of exclusion.

**Conclusions:** There is not a homogeneous pattern of food avoidance. Dietary restrictions should be based on a proven food allergy or intolerance. Dietary counseling should be based on sound nutritional knowledge.

PMID: 22732998 [PubMed - in process]

[http://www.journalofclinicalvirology.com/article/S1386-6532\(12\)0021...](http://www.journalofclinicalvirology.com/article/S1386-6532(12)0021...)

### **Antiviral therapy of two patients with chromosomally-integrated human herpesvirus-6A**

José G. Montoya, Michael N. Neely, Sudhir Gupta, Mitchell R. Lunn, Kristin S. Loomis, Joshua C. Pritchett, Bruce Polsky, Peter G. Medveczky

Received 2 April 2012; received in revised form 23 May 2012; accepted 24 May 2012. published online 09 July 2012

#### **Abstract**

**Background:** Human herpesvirus 6 (HHV-6) is a neurotropic virus implicated in central nervous system (CNS) dysfunction, multiple sclerosis, seizures and encephalitis. Inherited or “chromosomally integrated” HHV-6

(CIHHV-6) is a condition characterized by high DNA loads and germ line transmission of HHV-6 genomes, which are integrated into the telomere.

**Objectives:** We previously reported that integrated HHV-6 can be reactivated by trichostatin A in vitro. Therefore, we hypothesized that a broad array of neurological symptoms of CIHHV-6 patients may respond to antiviral drug treatment.

**Study design:** The patients have been treated with antiviral drugs and monitored for viral load, late mRNA, and clinical improvement.

**Results:** Antiviral therapy of two CIHHV patients resulted in successful clinical resolution. However, both patients relapsed on multiple occasions within 4–6 months of cessation of antiviral therapy.

**Conclusions:** Successful antiviral drug treatment suggests that clinical symptoms of these patients were due to symptomatic reactivation of CIHHV-6.

Alternatively, some CIHHV-6 patients may have a reduced resistance to community-acquired HHV-6 strains due to tolerance leading to persistent infections.

### **Intestinal microbiota in functional bowel disorders: a Rome foundation report**

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#### **+ Author Affiliations**

Professor Magnus Simren, Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg S-41345, Sweden; Contributors The Working Team was led by MS and GB. All working team members contributed equally to the manuscript.

#### **Abstract**

It is increasingly perceived that gut host–microbial interactions are important elements in the pathogenesis of functional gastrointestinal disorders (FGID).

The most convincing evidence to date is the finding that functional dyspepsia and irritable bowel syndrome (IBS) may develop in predisposed individuals following a bout of infectious gastroenteritis.

There has been a great deal of interest in the potential clinical and therapeutic implications of small intestinal bacterial overgrowth in IBS. However, this theory has generated much debate because the evidence is largely based on breath tests which have not been validated.

The introduction of culture-independent molecular techniques provides a major advancement in our understanding of the microbial community in FGID. Results from 16S rRNA-based microbiota profiling approaches demonstrate both quantitative and qualitative changes of mucosal and faecal gut microbiota, particularly in IBS.

Investigators are also starting to measure host–microbial interactions in IBS. The current working hypothesis is that abnormal microbiota activate mucosal innate immune responses which increase epithelial permeability, activate nociceptive sensory pathways and dysregulate the enteric nervous system.

While we await important insights in this field, the microbiota is already a therapeutic target.

Existing controlled trials of dietary manipulation, prebiotics, probiotics, synbiotics and non-absorbable antibiotics are promising, although most are limited by suboptimal design and small sample size.

In this article, the authors provide a critical review of current hypotheses regarding the pathogenetic involvement of microbiota in FGID and evaluate the results of microbiota-directed interventions.

The authors also provide clinical guidance on modulation of gut microbiota in IBS.

OPEN ACCESS Gut doi:10.1136/gutjnl-2012-302167 <http://gut.bmj.com/content/early/2012/07/09/gutjnl-2012-302167.long>

<http://www.ncbi.nlm.nih.gov/pubmed/22771174>

Psychiatry Res. 2012 Jul 6. [Epub ahead of print]

**Ultra-Slow delta power in chronic fatigue syndrome.**

Le Bon O, Neu D, Berquin Y, Lanquart JP, Hoffmann R, Mairesse O, Armitage R., Brugmann University Hospital, Sleep Laboratory and Unit for Chronobiology U78, Université Libre de Bruxelles (U.L.B.), Brussels, Belgium; Hôpital Erasme, Sleep Research Unit, Université Libre de Bruxelles (U.L.B.), Brussels, Belgium.

**Abstract**

The role of sleep in patients diagnosed with chronic fatigue syndrome is not fully understood.

Studies of polysomnographic and quantitative sleep electroencephalographic (EEG) measures have provided contradictory results, with few consistent findings in patients with Chronic Fatigue Syndrome (CFS). For the most part, it appears that delta EEG activity may provide the best discrimination between patients and healthy controls.

A closer examination of delta activity in the very slow end of the frequency band is still to be considered in assessing sleep in CFS. The present preliminary study compared absolute and relative spectral power in conventional EEG bands and ultra-slow delta (0.5-0.8Hz) between 10 young female patients with the CFS and healthy controls without psychopathology. In absolute measures, the ultra-slow delta power was lower in CFS, about one-fifth that of the control group. Other frequency bands did not differ between groups.

Relative ultra-slow delta power was lower in patients than in controls. CFS is associated with lower ultra-slow (0.5-0.8Hz) delta power, underscoring the importance of looking beyond conventional EEG frequency bands. From a neurophysiological standpoint, lower ultra-slow wave power may indicate abnormalities in the oscillations in membrane potential or a failure in neural recruitment in those with CFS.

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**The effect of dietary glutamate on fibromyalgia and irritable bowel symptoms.**

Holton KF, Taren DL, Thomson CA, Bennett RM, Jones KD., Departments of Orthopaedics and Rehabilitation, Oregon Health & Science University, Portland, OR, USA.

*Abstract*

**OBJECTIVES:** To examine the effects of a challenge with monosodium glutamate (MSG) as compared to placebo on the symptoms of fibromyalgia (FM), in participants who initially experienced >30% remission of symptoms on an excitotoxin elimination diet.

**METHODS:** Fifty-seven FM patients who also had irritable bowel syndrome (IBS) were placed on a 4-week diet that excluded dietary additive excitotoxins including MSG and aspartame. Thirty-seven people completed the diet and 84% of those reported that >30% of their symptoms resolved, thus making them eligible to proceed to challenges. Subjects who improved on the diet were then randomised to a 2-week double-blind placebo-controlled crossover challenge with MSG or placebo for 3 consecutive days each week.

The primary outcome measure was total symptom score. Secondary outcome measures included visual analogue pain scales (VAS for FM and IBS), an IBS Quality of Life Questionnaire (IBS QOL) and the Fibromyalgia Impact Questionnaire-Revised (FIQR). Repeated measures ANOVA was used to analyse crossover challenge results.

**RESULTS:** The MSG challenge, as compared to placebo, resulted in a significant return of symptoms (total symptom score,  $p<0.02$ ); a worsening of fibromyalgia severity as determined by the FIQR ( $p<0.03$ ); decreased quality of life in regards to IBS symptoms (IBS QOL,  $p<0.05$ ); and a non-significant trend toward worsening FM pain based on visual analogue scale (VAS,  $p<0.07$ ).

**CONCLUSIONS:** These findings suggest that dietary glutamate may be contributing to FM symptoms in some patients. Future research on the role of dietary excitotoxins in FM is warranted.

**Inflammatory and Cell-Mediated Immune Biomarkers in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Depression: Inflammatory Markers Are Higher in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome than in Depression**

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Psychother Psychosom 2012;81:286-295 (DOI: 10.1159/000336803)

**Abstract**

Background: Depression is an inflammatory disorder while many authors declare myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) to be a functional disorder. The aim of the present study is to compare inflammatory and cell-mediated immune (CMI) responses between depression and ME/CFS. Methods: We measured two proinflammatory cytokines (PICs) in plasma, interleukin-1 (IL-1) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), with enzyme-linked immunosorbent assays, and serum neopterin with a radioimmunoassay in controls, ME/CFS and depressive patients. Results: Plasma PICs were significantly higher in ME/CFS than in depression and higher in both patient groups than in controls.

Increased PIC levels in depression were attributable to the presence of fatigue and physio-somatic symptoms. Serum neopterin did not differ significantly between depression and ME/CFS but was higher in both patient groups than in controls. The significant positive correlations between neopterin and either IL-1 or TNF- $\alpha$  were significantly greater in depression than in ME/CFS. Conclusions: Since PICs cause depression-like behaviors and fatigue/malaise, we suggest that inflammation may play a role in the pathophysiology of ME/CFS and depression. Increased neopterin also seems to contribute to the pathophysiology of both disorders. This study has detected a shared 'pathway phenotype', i.e. disorders in inflammatory and CMI pathways, which underpins both ME/CFS and depression and, therefore, may explain the co-occurrence of both disorders. ME/CFS and depression are discriminated from each other by increased PICs in ME/CFS and differences in the immune cell communication networks.

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**Peripheral and Central Mechanisms of Fatigue in Inflammatory and Noninflammatory Rheumatic Diseases.**

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**Abstract**

Fatigue is a common symptom in a large number of medical and psychological disorders, including many rheumatologic illnesses. A frequent question for health care providers is related to whether reported fatigue is "in the mind" or "in the body"-that is, central or peripheral.

If fatigue occurs at rest without any exertion, this suggests psychological or central origins. If patients relate their fatigue mostly to physical activities, including exercise, their symptoms can be considered peripheral. However, most syndromes of fatigue seem to depend on both peripheral and central mechanisms.

Sometimes, muscle biopsy with histochemistry may be necessary for the appropriate tissue diagnosis, whereas serological tests generally provide little reliable information about the origin of muscle fatigue. Muscle function and peripheral fatigue can be quantified by contractile force and action potential measurements, whereas validated questionnaires are frequently used for assessment of mental fatigue.

Fatigue is a hallmark of many rheumatologic conditions, including fibromyalgia, myalgic encephalitis/chronic fatigue syndrome, rheumatoid arthritis, systemic lupus, Sjogren's syndrome, and ankylosing spondylitis. Whereas many studies have focused on disease activity as a correlate to these patients' fatigue, it has become apparent that other factors, including negative affect and pain, are some of the most powerful predictors for fatigue.

Conversely, sleep problems, including insomnia, seem to be less important for fatigue. There are several effective treatment strategies available for fatigued patients with rheumatologic disorders, including pharmacological and nonpharmacological therapies.

Med Hypotheses. 2012 Jul 12. [Epub ahead of print]

**Could cadmium be responsible for some of the neurological signs and symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.**

Pacini S, Fiore MG, Magherini S, Morucci G, Branca JJ, Gulisano M, Ruggiero M., University of Firenze, Italy.

**Abstract**

Exposure to heavy metals, with particular reference to mercury and gold in dental amalgams, has been considered among the triggers of ME/CFS.

Here we hypothesize that cadmium, a widespread occupational and environmental heavy metal pollutant, might be associated with some of the neurological findings described in ME/CFS. In fact, ME/CFS patients show a decrease of the volume of the gray matter in turn associated with objective reduction of physical activity.

Cadmium induces neuronal death in cortical neurons through a combined mechanism of apoptosis and necrosis and it could then be hypothesized that cadmium-induced neuronal cell death is responsible for some of the effects of cadmium on the central nervous system, i.e. a decrease in attention level and memory in exposed humans as well as to a diminished ability for training and learning in rats, that are symptoms typical of ME/CFS.

This hypothesis can be tested by measuring cadmium exposure in a cohort of ME/CFS patients compared with matched healthy controls, and by measuring gray matter volume in un-exposed healthy controls, exposed non-ME/CFS subjects, un-exposed ME/CFS patients and exposed ME/CFS patients.

In addition, we hypothesize that cadmium exposure could be associated with reduced cerebral blood flow in ME/CFS patients because of the disruptive effects of cadmium on angiogenesis. In fact, cadmium inhibits angiogenesis and low global cerebral flow is associated with abnormal brain neuroimaging results and brain dysfunction in the form of reduced cognitive testing scores in ME/CFS patients.

This hypothesis can be tested by measuring cerebral cortex blood flow in un-exposed healthy controls, exposed non-ME/CFS subjects, un-exposed ME/CFS patients and exposed ME/CFS patients.

If our hypothesis is demonstrated correct, the consequences could affect prevention, early diagnosis, and treatment of ME/CFS. Implications in early diagnosis could entail the evaluation of symptoms typical of ME/CFS in cadmium-exposed subjects as well as the search for signs of exposure to cadmium in subjects diagnosed with ME/CFS.

Nutritional supplementation of magnesium and zinc could then be considered, since these elements have been proposed in the prophylaxis and therapy of cadmium exposure, and magnesium was demonstrated effective on ME/CFS patients' symptom profiles.

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*Neuromolecular Med.* 2012 Jul 14. [Epub ahead of print]

**Lipidomic Profiling of Phosphocholine Containing Brain Lipids in Mice with Sensorimotor Deficits and Anxiety-Like Features After Exposure to Gulf War Agents.**

Abdullah L, Evans JE, Bishop A, Reed JM, Crynen G, Phillips J, Pelot R, Mullan MA, Ferro A, Mullan CM, Mullan MJ, Ait-Ghezala G, Crawford FC., Roskamp Institute, 2040 Whitfield Avenue, Sarasota, FL, 34243, USA.

**Abstract**

The central nervous system (CNS)-based symptoms of Gulf War Illness (GWI) include motor dysfunction, anxiety, and cognitive impairment. Gulf War (GW) agents, such as pyridostigmine bromide (PB), permethrin (PER), N,N-diethyl-meta-toluamide (DEET), and stress, are among the contributory factors to the pathobiology of GWI.

This study characterizes disturbances in phosphocholine-containing lipids that accompany neurobehavioral and neuropathological features associated with GW agent exposure.

Exposed mice received PB orally, dermal application of PER and DEET and restraint stress daily for 28 days, while controls received vehicle during this period. Neurobehavioral studies included the rotarod, open field, and Morris water maze tests.

Histopathological assessments included glial fibrillary acid protein, CD45, and Nissl staining. Liquid chromatography/mass spectrometry with source collision-induced dissociation in negative and positive ionization scanning modes was performed to characterize brain phosphatidylcholine (PC) and sphingomyelin (SM).

A significant increase in ether containing PC (ePC34:0, ePC36:2, and ePC36:1) or long-chain fatty acid-containing PC (38:1, 40:4, 40:2) was observed in exposed mice compared with controls. Among differentially expressed PCs, levels of those with monounsaturated fatty acids were more affected than those with saturated and polyunsaturated fatty acids.

Sensorimotor deficits and anxiety, together with an increase in astrocytosis, were observed in exposed mice compared with controls. These lipid changes suggest that alterations in peroxisomal pathways and stearoyl-CoA desaturase activity accompany neurobehavioral and neuropathological changes after GW agent exposure and represent possible treatment targets for the CNS symptoms of GWI.

J Psychosom Res. 2012 Aug;73(2):86-91. Epub 2012 Jun 20.

**Perceived injustice in fibromyalgia: Psychometric characteristics of the Injustice Experience Questionnaire and relationship with pain catastrophising and pain acceptance.**

Rodero B, Luciano JV, Montero-Marín J, Casanueva B, Palacin JC, Gili M, López Del Hoyo Y, Serrano-Blanco A, Garcia-Campayo J., Clínica Rodero, Santander, Spain.

*Abstract*

**OBJECTIVE:** To validate a Spanish version of the Injustice Experience Questionnaire (IEQ), a measure of perceived injustice, in a fibromyalgia sample and to examine its relationship with pain catastrophising and pain acceptance.

**METHODS:** The IEQ was administered along with the Pain Visual Analogue Scale, the Fibromyalgia Impact Questionnaire, the Hospital Anxiety and Depression Scale, the Pain Catastrophizing Scale (PCS) and the Chronic Pain Acceptance Questionnaire (CPAQ) to 250 primary care patients with fibromyalgia.

**RESULTS:** The IEQ had good test-retest reliability (intraclass correlation coefficient=0.98) and internal consistency (Cronbach's  $\alpha=0.92$ ). The factor structure obtained was similar to the original validation study. The multiple regression analyses showed that perceived injustice (PI) accounted for significant pain-related outcomes after controlling pain intensity, PCS and CPAQ. Principal component analysis of both the IEQ and the CPAQ taken together showed that the two constructs do not represent opposite extremes of the same dimension.

**CONCLUSION:** The IEQ is a reliable assessment tool for measuring PI among patients with fibromyalgia. PI seems to be distinct from catastrophising, although the two constructs are very similar. The factor analysis showed that PI and acceptance represent related constructs, and this entails relevant implications for therapy, as acceptance-based interventions would be appropriate.

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J Ethnopharmacol. 2012 Jul 5. [Epub ahead of print]

**Shilajit Attenuates Behavioral Symptoms of Chronic Fatigue Syndrome by Modulating the Hypothalamic-Pituitary-Adrenal Axis and Mitochondrial Bioenergetics in rats.**

Surapaneni DK, Adapa SR, Preeti K, Teja GR, Veeraragavan M, Krishnamurthy S., Neurotherapeutics lab, Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi- 221 005 U.P., India.

*Abstract*

**ETHNOPHARMACOLOGICAL RELEVANCE:** Shilajit has been used a rejuvenator for ages in Indian ancient traditional medicine and has been validated for a number of pharmacological activities.

**AIM OF THE STUDY:** The effect of processed shilajit which was standardized to dibenzo- $\alpha$ -pyrones (DBPs;0.43% w/w), DBP-chromoproteins (DCPs; 20.45% w/w) and fulvic acids (56.75% w/w) was evaluated in a rat model of chronic fatigue syndrome (CFS) in rats. The mitochondrial bioenergetics and the activity of hypothalamus-pituitary-adrenal (HPA) axis were evaluated for the plausible mechanism of action of shilajit.

**MATERIALS AND METHODS:** CFS was induced by forcing the rats to swim for 15mins for 21 consecutive days. The rats were treated with shilajit (25, 50 and 100mg/kg) for 21 days before exposure to stress procedure. The behavioral consequence of CFS was measured in terms of immobility and the climbing period. The post-CFS anxiety level was assessed by elevated plus maze (EPM) test. Plasma corticosterone and adrenal gland weight were estimated as indices of hypothalamus-pituitary-adrenal (HPA) axis activity. Analysis of mitochondrial complex chain enzymes (Complex I, II, IV and V) and mitochondrial membrane potential (MMP) in prefrontal cortex (PFC) were performed to evaluate the mitochondrial bioenergetics and integrity respectively.

**RESULTS:** Shilajit reversed the CFS-induced increase in immobility period and decrease in climbing behavior as well as attenuated anxiety in the EPM test. Shilajit reversed CFS-induced decrease in plasma corticosterone level and loss of adrenal gland weight indicating modulation of hypothalamus-pituitary-adrenal (HPA) axis. Shilajit prevented CFS-induced mitochondrial dysfunction by stabilizing the complex enzyme activities and the loss of MMP. Shilajit reversed CFS - induced mitochondrial oxidative stress in terms of NO concentration and, LPO, SOD and catalase activities.

**CONCLUSION:** The results indicate that shilajit mitigates the effects of CFS in this model possibly through the modulation of HPA axis and preservation of mitochondrial function and integrity. The reversal of CFS-induced behavioral symptoms and mitochondrial bioenergetics by shilajit indicates mitochondria as a potential target for treatment of CFS.

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Arthritis Res Ther. 2012 Jul 9;14(4):R162. [Epub ahead of print]

**Changes in pain and insulin-like growth factor 1 in fibromyalgia during exercise: the involvement of cerebrospinal inflammatory factors and neuropeptides.**

Bjersing JL, Dehlin M, Erlandsson M, Bokarewa M, Mannerkorpi K.

**ABSTRACT:**

**INTRODUCTION:** Fibromyalgia (FM) is characterized by chronic pain. Impaired growth hormone responses and reduced serum insulin-like growth factor 1 (IGF-1) are common in FM. The aim was to examine changes in serum IGF-1, cerebrospinal fluid (CSF), neuropeptides and cytokines during aerobic exercise in FM patients.

**METHOD:** A total of 49 patients (median age 52 years) with FM were included in the study. They were randomized to either the moderate-to-high intensity Nordic Walking (NW) program (n=26) or the supervised low-intensity walking (LIW) program (n=23). Patients participated in blood tests before and after 15-weeks of aerobic exercise. Changes in serum levels of free IGF-1, pain rating on a 0-100 mm scale, pain threshold and 6-minute walk test (6MWT) were examined. CSF, neuropeptides, matrix metalloproteinase 3 (MMP-3) and inflammatory cytokines were determined. Non-parametric tests were used for group comparisons and correlation analyses.

**RESULTS:** Serum free IGF-1 levels did not change during 15-weeks of exercise between the two groups, although the 6MWT significantly improved in the NW-group ( $p=0.033$ ) when compared to LIW.

Pain did not significantly change in any of the groups, but tended to decrease ( $p=0.052$ ) over time in the total group. There was a tendency towards a correlation between baseline IGF-1 and an decrease of pain in response to exercise ( $r=0.278$ ,  $p=0.059$ ). When adjusted for age this tendency disappeared.

The change in serum free IGF-1 correlated positively with an alteration in CSF substance P (SP) levels ( $r_s=0.495$ ,  $p=0.072$ ), neuropeptide Y (NPY) ( $r_s=0.802$ ,  $p=0.001$ ), and pain threshold ( $r_s=0.276$ ,  $p=0.058$ ). Differing CSF SP levels correlated positively to a change in pain threshold ( $r_s=0.600$ ,  $p=0.023$ ), while the shift in CSF MMP-3 inversely correlated with an altered pain threshold ( $r_s=-0.569$ ,  $p=0.034$ ).

**CONCLUSIONS:** The baseline level of serum free IGF-1 did not change during high or low-intensity of aerobic exercise. Changes in IGF-1 correlated positively with a variation in CSF SP, NPY and pain threshold. These data indicate a beneficial role of IGF-1 during exercise in FM.

<http://clinicaltrials.gov/ct2/show/NCT00643006>

<http://www.ncbi.nlm.nih.gov/pubmed/22760464>

Schmerz. 2012 Jun;26(3):311-7.

**Complementary and alternative therapies for fibromyalgia syndrome : Systematic review, meta-analysis and guideline.**

[Article in German]

Langhorst J, Häuser W, Bernardy K, Lucius H, Settan M, Winkelmann A, Musial F., SourceInnere Medizin V (Naturheilkunde und Integrative Medizin), Kliniken Essen-Mitte, Am Deimelsberg 34a, 45276, Essen, Deutschland.

**Abstract**

**BACKGROUND:** The scheduled update to the German S3 guidelines on fibromyalgia syndrome (FMS) by the Association of the Scientific Medical Societies ("Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften", AWMF; registration number 041/004) was planned starting in March 2011.

**MATERIALS AND METHODS:** The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy ("Deutsche Interdisziplinären Vereinigung für Schmerztherapie", DIVS), 9 scientific medical societies and 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, PsycInfo, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Centre for Evidence-Based Medicine. The recommendations were based on level of evidence, efficacy (meta-analysis of the outcomes pain, sleep, fatigue and health-related quality of life), acceptability (total dropout rate), risks (adverse events) and applicability of treatment modalities in the German health care system. The formulation and grading of recommendations was accomplished using a multi-step, formal consensus process. The guidelines were reviewed by the boards of the participating scientific medical societies.

**RESULTS AND CONCLUSION:** Meditative movement therapies (qi gong, tai chi, yoga) are strongly recommended. Acupuncture can be considered. Mindfulness-based stress reduction as monotherapy and dance therapy as monotherapy are not recommended. Homeopathy is not recommended. In a minority vote, homeopathy was rated as "can be considered". Nutritional supplements and reiki are not recommended. The English full-text version of this article is available at SpringerLink (under "Supplemental").

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## Dysfunctional Endogenous Analgesia During Exercise in Patients with Chronic Pain: To Exercise or Not to Exercise?

### Part 1 of 2 parts

Jo Nijs, PhD, Eva Kosek, MD, PhD, Jessica Van Oosterwijck, PhD and Mira Meeus, PhD

**Background:** Exercise is an effective treatment for various chronic pain disorders, including fibromyalgia, chronic neck pain, osteoarthritis, rheumatoid arthritis, and chronic low back pain.

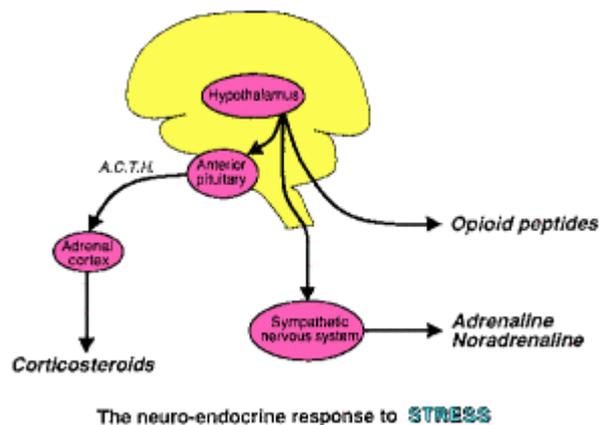
Although the clinical benefits of exercise therapy in these populations are well established (i.e. evidence based), it is currently unclear whether exercise has positive effects on the processes involved in chronic pain (e.g. central pain modulation).

**Objectives:** Reviewing the available evidence addressing the effects of exercise on central pain modulation in patients with chronic pain.

**Methods:** Narrative review.

**Results:** Exercise activates endogenous analgesia (EA) in healthy individuals. The increased pain threshold following exercise is due to the release of endogenous opioids and activation of (supra)spinal nociceptive inhibitory mechanisms orchestrated by the brain. Exercise triggers the release of  $\beta$ -endorphins from the pituitary (peripherally) and the hypothalamus (centrally), which in turn enables analgesic effects by activating  $\mu$ -opioid receptors peripherally and centrally, respectively. The hypothalamus, through its projections on the periaqueductal grey, has the capacity to activate descending nociceptive inhibitory mechanisms.

However, several groups have shown dysfunctioning of endogenous analgesia in response to exercise in patients with chronic pain. Muscle contractions activate generalized endogenous analgesia in healthy, pain-free humans and patients with either osteoarthritis or rheumatoid arthritis, but result in increased generalised pain sensitivity in fibromyalgia patients.



### Part 2 of 2 parts

In patients having local muscular pain (e.g. shoulder myalgia), exercising non-painful muscles activates generalized endogenous analgesia. However, exercising painful muscles does not change pain sensitivity either in the exercising muscle or at distant locations.

The dysfunctional EA in response to aerobic exercise was first shown in a small study of patients with chronic fatigue syndrome and healthy controls in which participants performed a graded exercise with 3 stages on a treadmill. Every stage of the exercise consisted of 5 minutes walking at a constant pace of 5km/h, with an increasing incline of 5°. Dysfunctional EA was demonstrated by decreased pain thresholds following exercise in patients with chronic fatigue syndrome, while pain thresholds increased in healthy controls. These findings were later replicated in 2 larger studies using various types of exercise. From these studies it is concluded that neither types of aerobic exercise were able to activate EA in patients with chronic fatigue syndrome who experience chronic widespread pain.

Importantly, the dysfunctional EA partly explains symptom flares following exercise in patients with chronic fatigue syndrome having chronic widespread pain.

It is concluded that the dysfunctional EA during aerobic exercise is not characteristic for all chronic pain patients, but rather limited to those with clear evidence of central sensitization (e.g. chronic whiplash, fibromyalgia, chronic fatigue syndrome).

The reviewed studies examined acute effects of exercise rather than long-term effects of exercise therapy. The studies summarized address acute bouts of exercise, not findings from randomized clinical trials examining the effects of exercise as a therapeutic intervention. The studies showing dysfunctional EA during exercise in some chronic pain conditions do not contradict the clinical evidence favoring the use of exercise as an intervention for chronic pain.

**Conclusions:** A dysfunctional response of patients with chronic pain and aberrations in central pain modulation to exercise has been shown, indicating that exercise therapy should be individually tailored with emphasis on prevention of symptom flares.

The paper discusses the translation of these findings to rehabilitation practice together with future research avenues.

Pain Physician 2012; 15:ES205-ES213

J Pain Res. 2012;5:193-201. Epub 2012 Jun 22.

**Predictors of duloxetine adherence and persistence in patients with fibromyalgia.**

Cui Z, Zhao Y, Novick D, Faries D., Eli Lilly and Company, Indianapolis, IN, USA.

*Abstract*

**OBJECTIVES:** Adherence to medication for the treatment of fibromyalgia (FM) is predictive of lower overall health-care costs, and thus a lower burden on both patients and providers. The objectives of this study were to examine the predictors of adherence to and persistence with duloxetine therapy among commercially insured FM patients, and to identify subgroups of patients with high duloxetine persistence and adherence.

**STUDY DESIGN:** This cross-sectional, retrospective study analyzed medical and pharmacy records over 1 year for patients in the US aged 18-64 years with FM who initiated (no prior 90-day use) duloxetine treatment in 2008.

**METHODS:** Adherence to duloxetine was measured by medication possession ratio (MPR), with high adherence defined as  $MPR \geq 0.8$ . Persistence was defined as the duration of therapy from the index date to the earliest

of: the ending date of the last prescription, the date of the first gap of >15 days between prescriptions, or the end of the study period (12 months). Demographic and clinical predictors of adherence were examined via multiple logistic regression (MLR), and subgroups of duloxetine-persistent and -adherent patients were identified using classification and regression trees (CART).

**RESULTS:** Among 4660 duloxetine patients, 33% achieved high adherence. Factors associated with high adherence from MLR included older age, North Central and Northeast regions, prior venlafaxine, pregabalin, selective serotonin reuptake inhibitor (SSRI), or other antidepressant use, or comorbid dyslipidemia or osteoarthritis (all  $P < 0.05$ ). CART analysis revealed that patients with prior antidepressant use, aged  $\geq 46$ , or prior osteoarthritis had higher MPR (all  $P < 0.05$ ), and patients aged  $\geq 45$  with a history of SSRI, venlafaxine, or anticonvulsant use had longer duration of therapy (all  $P < 0.05$ ).

**CONCLUSIONS:** Patients with high adherence to and persistence with duloxetine were significantly older and had prior antidepressant use.

Clin Pediatr (Phila). 2012 Jul 31. [Epub ahead of print]

**Orthostatic Tolerance Testing in a Prospective Cohort of Adolescents With Chronic Fatigue Syndrome and Recovered Controls Following Infectious Mononucleosis.**

Katz BZ, Stewart JM, Shiraishi Y, Mears CJ, Taylor R.

**Abstract**

Chronic fatigue syndrome (CFS) is a complex condition responsible for marked functional impairment.

The authors recently reported that 6 months following acute infectious mononucleosis (IM), 13% of adolescents met criteria for CFS. The authors' objective was to assess standing orthostatic tolerance (SOT) in adolescents with CFS and in controls 6 months following IM.

In all, 36 of 39 adolescents diagnosed with CFS 6 months following IM and 43 of 50 recovered controls had SOT testing (SOTT) performed.  $\chi^2$  Analysis was performed to study the relationships between SOTT and the diagnosis of CFS. Adolescents diagnosed with CFS and recovered controls did not differ significantly in age, weight, or body mass index.

The authors found that 9 of 36 adolescents with CFS (25%) versus 9 of 43 recovered controls (21%) had an abnormal SOTT, which was not a statistically significant difference. Adolescents who meet criteria for CFS 6 months following IM do not have, as a group, more standing orthostatic intolerance than recovered controls.

PMID: 22850676 [PubMed - as supplied by publisher]

## **Adaptive Pacing, Cognitive Behaviour Therapy, Graded Exercise, and Specialist Medical Care for Chronic Fatigue Syndrome: A Cost-Effectiveness Analysis**

Paul McCrone<sup>1\*</sup>, Michael Sharpe<sup>2</sup>, Trudie Chalder<sup>3</sup>, Martin Knapp<sup>1,4</sup>, Anthony L. Johnson<sup>5,6</sup>, Kimberley A. Goldsmith<sup>7</sup>, Peter D. White<sup>8</sup>

**Background** The PACE trial compared the effectiveness of adding adaptive pacing therapy (APT), cognitive behaviour therapy (CBT), or graded exercise therapy (GET), to specialist medical care (SMC) for patients with chronic fatigue syndrome. This paper reports the relative cost-effectiveness of these treatments in terms of quality adjusted life years (QALYs) and improvements in fatigue and physical function.

**Methods** Resource use was measured and costs calculated. Healthcare and societal costs (healthcare plus lost production and unpaid informal care) were combined with QALYs gained, and changes in fatigue and disability; incremental cost-effectiveness ratios (ICERs) were computed.

**Results** SMC patients had significantly lower healthcare costs than those receiving APT, CBT and GET. If society is willing to value a QALY at £30,000 there is a 62.7% likelihood that CBT is the most cost-effective therapy, a 26.8% likelihood that GET is most cost effective, 2.6% that APT is most cost-effective and 7.9% that SMC alone is most cost-effective.

Compared to SMC alone, the incremental healthcare cost per QALY was £18,374 for CBT, £23,615 for GET and £55,235 for APT. From a societal perspective CBT has a 59.5% likelihood of being the most cost-effective, GET 34.8%, APT 0.2% and SMC alone 5.5%. CBT and GET dominated SMC, while APT had a cost per QALY of £127,047. ICERs using reductions in fatigue and disability as outcomes largely mirrored these findings.

**Conclusions** Comparing the four treatments using a health care perspective, CBT had the greatest probability of being the most cost-effective followed by GET. APT had a lower probability of being the most cost-effective option than SMC alone. The relative cost-effectiveness was even greater from a societal perspective as additional cost savings due to reduced need for informal care were likely.

The full study can be found here: <http://www.plosone.org/article/info:doi/10.1371/journal.pone.0040808>

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**Depressive symptoms and pragmatic rehabilitation for chronic fatigue syndrome.**

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**Abstract**

**BACKGROUND:** Previous research has suggested that depressed mood may predict outcome and moderate response to treatment in chronic fatigue syndrome, although findings have differed between studies.

**AIMS:** To examine potential moderators of response to pragmatic rehabilitation v. general practitioner treatment as usual in a recent randomised trial for patients with chronic fatigue syndrome in primary care (IRCTN74156610 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2859122/?tool=pubmed>).

**METHOD:** Simple regressions, with weighting adjustments to allow for missing data, were calculated. Demographic, medical and psychological variables, and treatment arm, were entered separately and as an interaction term. The outcome variable in each case was change in Chalder Fatigue Scale scores, from baseline to 1-year follow-up, our primary outcome point.

**RESULTS:** Longer illness durations predicted poorer outcome across the two treatment arms. For patients allocated to pragmatic rehabilitation compared with those allocated to treatment as usual, higher levels of depressive symptoms at baseline were associated with smaller improvements in fatigue ( $P = 0.022$ ).

**CONCLUSIONS:** For patients in primary care with higher levels of depressive symptoms, either more intensive or longer pragmatic rehabilitation, or cognitive-behavioural therapy, may be required in order to show a significant improvement in fatigue.

PMID: 22844025 [PubMed - as supplied by publisher]

### **Meta analysis of CBT in fibromyalgia**

Reumatismo. 2012 Jul 19;64(3):151-7. doi: 10.4081/reumatismo.2012.151. [Article in Italian]

Minelli A, Vaona A.

#### **Abstract**

Fibromyalgia (FM) is a chronic disorder caused by a dysfunction of central nervous system sensitization. This syndrome is characterized by widespread pain and diffuse tenderness, but often also presents fatigue, sleep disturbances, and a whole range of symptoms such as morning stiffness, decreased physical function and dyscognition.

FM is usually treated with pharmacological and non-pharmacological treatments. The non-pharmacological interventions include cognitive behavioral therapy (CBT), physiotherapy, acupuncture and patient education programs.

In order to evaluate the efficacy of CBT and compare it with other non-pharmacological treatments, we performed a review of the meta-analytic literature. We evaluated the methodological quality of publications found by following the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

Data showed that CBT does not provide better results than other non-pharmacological treatments on outcomes of pain, fatigue, sleep disturbance and quality of life, at either a short or long-term evaluation.

On the contrary, CBT seems to be more effective on symptoms of depression for a short period, whereas it considerably improves the pain self-management and reduces the number of visits to the doctor.

The data currently available indicate that cost-effectiveness studies could help us to understand whether the reduction in the number of visits to the doctor could balance the cost of CBT to the health public system.