

Scand J Rheumatol. 2015 Aug 14:1-8. [Epub ahead of print]

**Endogenous event-related potentials in patients with primary Sjögren's syndrome without central nervous system involvement.**

Dziadkowiak E, Sebastian A, Wiland P, Waliszewska-Prosół M, Wieczorek M, Zagrajek M, Ejma M.

**Abstract**

**OBJECTIVES:** Endogenous cognitive event-related potentials (CERPs) reflect higher-level processing of sensory information and can be used to evaluate cognitive functions. The aim of this paper was to determine whether there are any abnormalities in the electrophysiological parameters of CERPs in patients with primary Sjögren's syndrome (pSS) but without symptoms of central nervous system (CNS) involvement or mental disorder. The analysis of CERP parameters was then correlated with the clinical status of the patients and with some of the immunological parameters in the patient group.

**METHOD:** Thirty consecutive patients with pSS (29 females, one male) were included in the study. All the patients underwent CERP examination.

**RESULTS:** There was a significant prolongation of the latency of P300 and N200 potentials in patients with pSS. Abnormalities in electrophysiological parameters of CERPs correlated with the duration of the disease, salivary gland abnormalities, and elevated erythrocyte sedimentation rate (ESR) values. Patients with coexisting chronic fatigue syndrome (CFS) had larger P300 amplitudes. There were no statistically significant changes in the electrophysiological parameters of CERPs in patients with pSS dependent on the presence of peripheral nervous system (PNS) lesions, skin changes, arthritis, abnormalities in white blood cells and the immune system or the levels of blood lipids.

**CONCLUSIONS:** The results of the study suggest the presence of a minor cognitive dysfunction in patients with pSS without symptoms of CNS involvement or mental disorder. Cognitive dysfunction correlated with the disease duration time and the severity of inflammatory changes (salivary gland abnormalities and inflammatory markers in the blood). Further and larger longitudinal studies are necessary for confirmation of this correlation.

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Clin Rheumatol. 2015 Aug 15. [Epub ahead of print]

**The prevalence of severe fatigue in rheumatic diseases: an international study.**

Overman CL, Kool MB, Da Silva JA, Geenen R.

**Abstract**

Fatigue is a common, disabling, and difficult-to-manage problem in rheumatic diseases. Prevalence estimates of fatigue within rheumatic diseases vary considerably. Data on the prevalence of severe fatigue across multiple rheumatic diseases using a similar instrument is missing. Our aim was to provide an overview of the prevalence of severe fatigue across a broad range of rheumatic diseases and to examine its association with clinical and demographic variables.

Online questionnaires were filled out by an international sample of 6120 patients (88 % female, mean age 47) encompassing 30 different rheumatic diseases.

Fatigue was measured with the RAND(SF)-36 Vitality scale. A score of  $\leq 35$  was taken as representing severe fatigue (90 % sensitivity and 81 % specificity for chronic fatigue syndrome).

Severe fatigue was present in 41 to 57 % of patients with a single inflammatory rheumatic disease such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Sjögren's syndrome, psoriatic arthritis, and scleroderma. Severe fatigue was least prevalent in patients with osteoarthritis (35 %) and most prevalent in patients with fibromyalgia (82 %).

In logistic regression analysis, severe fatigue was associated with having fibromyalgia, having multiple rheumatic diseases without fibromyalgia, younger age, lower education, and language (French: highest prevalence; Dutch: lowest prevalence).

In conclusion, one out of every two patients with a rheumatic disease is severely fatigued. As severe fatigue is detrimental to the patient, the near environment, and society at large, unraveling the underlying mechanisms of fatigue and developing optimal treatment should be top priorities in rheumatologic research and practice.

PMID:26272057 [PubMed - as supplied by publisher]

**Polymorphism in COMT is associated with IgG3 subclass level and susceptibility to infection in patients with chronic fatigue syndrome.**

Löbel M, Mooslechner AA, Bauer S, Günther S, Letsch A, Hanitsch LG, Grabowski P, Meisel C, Volk HD, Scheibenbogen C.

**Abstract**

**BACKGROUND:** Chronic fatigue syndrome (CFS) is considered as a neuroimmunological disease but the etiology and pathophysiology is poorly understood. Patients suffer from sustained exhaustion, cognitive impairment and an increased sensitivity to pain and sensory stimuli. A subset of patients has frequent respiratory tract infections (RRTI).

Dysregulation of the sympathetic nervous system and an association with genetic variations in the catechol-O-methyltransferase (COMT) and glucocorticoid receptor genes influencing sympathetic and glucocorticoid metabolism were reported in CFS. Here, we analyzed the prevalence of SNPs of COMT and glucocorticoid receptor-associated genes in CFS patients and correlated them to immunoglobulin levels and susceptibility to RRTI.

**METHODS:** We analyzed blood cells of 74 CFS patients and 76 healthy controls for polymorphisms in COMT, FKBP5 and CRHR1 by allelic discrimination PCR. Serum immunoglobulins were determined by immunoturbidimetric technique, cortisol levels by ECLIA.

**RESULTS:** Contrary to previous reports, we found no difference between CFS patients and healthy controls in the prevalence of SNPs for COMT, FKBP5 and CRHR1. In patients with the Met/Met variant of COMT rs4680 we observed enhanced cortisol levels providing evidence for its functional relevance.

Both enhanced IgE and diminished IgG3 levels and an increased susceptibility to RRTI were observed in CFS patients with the Met/Met variant. Such an association was not observed in 68 non-CFS patients with RRTI.

**CONCLUSION:** Our results indicate a relationship of COMT polymorphism rs4680 with immune dysregulation in CFS providing a potential link for the association between stress and infection susceptibility in CFS.

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**A comparison of patients with Q fever fatigue syndrome and patients with chronic fatigue syndrome with a focus on inflammatory markers and possible fatigue perpetuating cognitions and behaviour.**

Keijmel SP, Saxe J, van der Meer JW, Nikolaus S, Netea MG, Bleijenberg G, Bleeker-Rovers CP, Knoop H.

**Abstract**

**OBJECTIVE:** Comparison of Q fever fatigue syndrome (QFS) and chronic fatigue syndrome (CFS) patients, with a focus on markers of inflammation and fatigue-related cognitive-behavioural variables.

**METHODS:** Data from two independent prospective studies on QFS (n=117) and CFS (n=173), respectively, were pooled and analyzed.

**RESULTS:** QFS patients were less often female, had a higher BMI, and had less often received treatment for depression before the onset of symptoms. After controlling for symptom duration and correcting for differences in diagnostic criteria for QFS and CFS with respect to the level of impairment and the presence of additional symptoms, differences in the proportion of females and BMI remained significant. After correction, QFS patients were also significantly older. In all analyses QFS patients were as fatigued and distressed as CFS patients, but reported less additional symptoms. QFS patients had stronger somatic attributions, and higher levels of physical activity. No differences were found with regard to inflammatory markers and in other fatigue-related cognitive-behavioural variables. The relationship between cognitive-behavioural variables and fatigue, previously established in CFS, could not be confirmed in QFS patients with the exception of the negative relationship between physical activity and fatigue.

**CONCLUSION:** Differences and similarities between QFS and CFS patients were found. Although the relationship between perpetuating factors and fatigue previously established in CFS could not be confirmed in QFS patients, the considerable overlap in fatigue-related cognitive-behavioural variables and the relationship found between physical activity and fatigue may suggest that behavioural interventions could reduce fatigue severity in QFS patients.

## **Two of Nation's Leading Chronic Fatigue Syndrome Experts Partner To Quantify the Disease Combining 40 years of clinical and research experience**

Two of the nation's leading experts on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—Bateman Horne Center Chief Medical Officer Dr. Lucinda Bateman, MD and Researcher Dr. Suzanne D. Vernon, PhD—announce their partnership to quantify diagnostic criteria recommended by the Institute of Medicine (IOM) of the National Academy of Sciences.

Dr. Bateman was a member of the IOM Committee that penned the 304-page report *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*. Released in February 2015, the report recommended diagnostic criteria for the main disease symptoms: fatigue that impairs normal activity, post-exertional malaise, unrefreshing sleep, cognitive impairment and orthostatic intolerance.

"If we are ever to mainstream medical care for the millions who suffer terribly from this disease," says Dr. Bateman, "there must be diagnostic tests. Dr. Vernon's experience in identifying biomarkers, establishing biobanks and cost-effectively gathering large amounts of real-life, real-time data will close in on this reality."

Dr. Vernon will spend the next several months finalizing the research initiative's design with data collection and analysis continuing into 2016 and beyond. "I've had great success recruiting innovative partners and rock star scientists into ME/CFS research," says Dr. Vernon. "Now Dr. Bateman and I will establish Bateman Horne Center as a center of excellence for research and clinical care."

### **DR. LUCINDA BATEMAN, BATEMAN**

While watching her sister suffer from Fibromyalgia and ME/CFS, Lucinda Bateman, MD, chose to dedicate her career to uncovering the clinical mysteries of these diseases. Now with more than 25 years of research and clinical experience, Dr. Bateman is a nationally recognized clinical expert on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and the Founder and Chief Medical Officer of Bateman Horne Center of Excellence for the medical advancement and treatment of Fibromyalgia and ME/CFS. Dr. Bateman attended The Johns Hopkins School of Medicine Class of 1987 and completed her Internal Medicine Residency at the University of Utah Health Sciences Center.

### **SUZANNE VERNON, PhD**

Suzanne D. Vernon, PhD, is the nation's leading researcher in ME/CFS, having raised millions of dollars for research studies that have resulted in more than 85 research papers and several international presentations to promote research and collaboration. Vernon earned her PhD in virology at the University of Wisconsin, Madison and was awarded a National Science Foundation post-doctoral fellowship at the U.S. Centers for Disease Control and Prevention (CDC). Vernon was appointed a team leader Research Microbiologist and led the ME/CFS laboratory program for 10 years. In 2007, Vernon became the first scientific director for the non-profit patient advocacy organization Solve ME/CFS Initiative.

**Testing the efficacy of web-based cognitive behavioural therapy for adult patients with chronic fatigue syndrome (CBIT): study protocol for a randomized controlled trial**

Anthonie Janse, Margreet Worm-Smeitink, José Bussel-Lagarde, Gijs Bleijenberg, Stephanie Nikolaus and Hans Knoop

BMC Neurology 2015, 15:137 doi:10.1186/s12883-015-0392-3

**Abstract**

**Background:** Cognitive behavioural therapy (CBT) is an effective treatment for fatigue and disabilities in patients with chronic fatigue syndrome (CFS). However, treatment capacity is limited.

Providing web-based CBT and tailoring the amount of contact with the therapist to the individual needs of the patient may increase the efficiency of the intervention. Web-based CBT for adolescents with CFS has proven to be effective in reducing fatigue and increasing school attendance.

In the proposed study the efficacy of a web-based CBT intervention for adult patients with CFS will be explored. Two different formats of web-based CBT will be tested. In the first format named protocol driven feedback, patients report on their progress and receive feedback from a therapist according to a preset schedule.

In the second format named support on demand, feedback and support of the therapist is only given when patients ask for it. The primary objective of the study is to determine the efficacy of a web-based CBT intervention on fatigue severity.

**Method/Design:** A randomized clinical trial will be conducted. Two-hundred-forty adults who have been diagnosed with CFS according to the US Centers for Disease Control and Prevention (CDC) consensus criteria will be recruited and randomized to one of three conditions: web-based CBT with protocol driven feedback, web-based CBT with support on demand, or wait list.

Feedback will be delivered by therapists specialized in CBT for CFS. Each of the web-based CBT interventions will be compared to a wait list condition with respect to its effect on the primary outcome measure; fatigue severity.

Secondary outcome measures are level of disability, physical functioning, psychological distress, and the proportion of patients with clinical significant improvement in fatigue severity. Outcomes will be assessed at baseline and six months post randomization. The web-based CBT formats will be compared with respect to the time therapists need to deliver the intervention.

**Discussion:** As far as we know this is the first randomized controlled trial (RCT) that evaluates the efficacy of a web-based CBT intervention for adult patients with CFS.

Trial registration  
NTR4013

<http://www.ncbi.nlm.nih.gov/pubmed/26242228>

Am J Clin Dermatol. 2015 Aug 5. [Epub ahead of print]

**The Dermatological Manifestations of Postural Tachycardia Syndrome: A Review with Illustrated Cases.**

Huang H, Hohler AD.

**Abstract**

Postural tachycardia syndrome (POTS) is a syndrome of excessive tachycardia with orthostatic challenge, and relief of such symptoms with recumbence.

There are several proposed subtypes of the syndrome, each with unique pathophysiology. Numerous symptoms such as excessive tachycardia, lightheadedness, blurry vision, weakness, fatigue, palpitations, chest pain, and tremulousness are associated with orthostatic intolerance.

Other co-morbid conditions associated with POTS are not clearly attributable to orthostatic intolerance. These include chronic headache, fibromyalgia, functional gastrointestinal or bladder disorders, cognitive impairment, and sleep disturbances.

Dermatological manifestations of POTS are also common and wide ranging, from livedo reticularis to Raynaud's phenomenon, from cutaneous flushing to erythromelalgia.

Here, we provide three illustrative cases of POTS with dermatological manifestations. We discuss the potential pathophysiology underlying such dermatological manifestations, and how such mechanisms could in turn help guide development of management.

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# Reflections on the Institute of Medicine's systemic exertion intolerance disease

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## **Abstract**

The Institute of Medicine (IOM) in the United States has recently proposed that the term systemic exertion intolerance disease (SEID) replace chronic fatigue syndrome. In addition, the IOM proposed a new case definition for SEID, which includes substantial reductions or impairments in the ability to engage in pre-illness activities, unrefreshing sleep, postexertional malaise, and either cognitive impairment or orthostatic intolerance. Unfortunately, these recommendations for a name change were not vetted with patient and professional audiences, and the new criteria were not evaluated with data sets of patients and controls. A recent poll suggests that the majority of patients reject this new name. In addition, studies have found that prevalence rates will dramatically increase with the new criteria, particularly due to the ambiguity revolving around exclusionary illnesses. Findings suggest that the new criteria select more patients who have less impairment and fewer symptoms than several other criteria. The implications of these findings are discussed in the current review.



# Cognitive dysfunction in adolescents with chronic fatigue: a cross-sectional study

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## ABSTRACT

**Objective** To compare cognitive function in adolescents with chronic fatigue with cognitive function in healthy controls (HC). **Study design** Cross-sectional study. **Setting** Paediatric department at Oslo University Hospital, Norway.

**Participants** 120 adolescents with chronic fatigue (average age 15.4 years; range 12–18) and 39 HC (average age 15.2 years; range 12–18).

**Methods** The adolescents completed a neurocognitive test battery measuring processing speed, working memory, cognitive inhibition, cognitive flexibility, verbal learning and verbal memory, and questionnaires addressing demographic data, depression symptoms, anxiety traits, fatigue and sleep problems. Parents completed the Behaviour Rating Inventory of Executive Function (BRIEF), which measures the everyday executive functions of children.

**Results** Adolescents with chronic fatigue had impaired cognitive function compared to HC regarding processing speed (mean difference 3.3, 95% CI 1.1 to 5.5,  $p=0.003$ ), working memory ( $-2.4$ ,  $-3.7$  to  $-1.1$ ,  $p<0.001$ ), cognitive inhibition response time (6.2, 0.8 to 11.7,  $p=0.025$ ) and verbal learning ( $-1.7$ ,  $-3.2$  to  $-0.3$ ,  $p=0.022$ ).

The BRIEF results indicated that everyday executive functions were significantly worse in the chronic fatigue group compared to the HC (11.2, 8.2 to 14.3,  $p<0.001$ ). Group differences remained largely unaffected when adjusted for symptoms of depression, anxiety traits and sleep problems.

**Conclusions** Adolescents with chronic fatigue had impaired cognitive function of clinical relevance, measured by objective cognitive tests, in comparison to HC. Working memory and processing speed may represent core difficulties.

## Plasma cytokine expression in adolescent chronic fatigue syndrome

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Chronic fatigue syndrome (CFS) is a prevalent and disabling condition among adolescents. The pathophysiology is poorly understood, but low-grade systemic inflammation has been suggested as an important component. This study compared circulating levels of individual cytokines and parameters of cytokine networks in a large set of adolescent CFS patients and healthy controls, and explored associations between cytokines and symptoms in the CFS group.

CFS patients (12–18 years old) were recruited nation-wide to a single referral center as part of the Nor-CAPITAL project (ClinicalTrials ID: NCT01040429). A broad case definition of CFS was applied, requiring three months of unexplained, disabling chronic/relapsing fatigue of new onset, whereas no accompanying symptoms were necessary. Thus, the case definition was broader than the Fukuda-criteria of CFS.

Healthy controls having comparable distribution of gender and age were recruited from local schools.

Twenty-seven plasma cytokines, including interleukins, chemokines and growth factors were assayed using multiplex technology. The results were subjected to network analyses using the ARACNE algorithm.

Symptoms were charted by a questionnaire, and patients were subgrouped according to the Fukuda-criteria.

A total of 120 CFS patients and 68 healthy controls were included. CFS patients had higher scores for fatigue ( $p < 0.001$ ) and inflammatory symptoms ( $p < 0.001$ ) than healthy controls. All cytokine levels

and cytokine network parameters were similar, and none of the differences were statistically different across the two groups, also when adjusting for adherence to the Fukuda criteria of CFS. Within the CFS group, there were no associations between aggregate cytokine network parameters and symptom scores.

Adolescent CFS patients are burdened by symptoms that might suggest low-grade systemic inflammation, but plasma levels of individual cytokines as well as cytokine network measures were not different from healthy controls, and there were no associations between symptoms and cytokine expression in the CFS group. Low-grade systemic inflammation does not appear to be a central part of adolescent CFS pathophysiology.

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## Abstract

**OBJECTIVE.** The objective of this study was to evaluate the effectiveness of an activity pacing self-management (APSM) intervention in improving performance of daily life activities in women with chronic fatigue syndrome (CFS).

**METHOD.** A total of 33 women with CFS (age  $41.1 \pm 11.2$  yr) were randomly allocated to APSM (experimental group;  $n = 16$ ) or relaxation (control group;  $n = 17$ ). Main outcome measures included the Canadian Occupational Performance Measure (COPM; primary) and Checklist Individual Strength (CIS).

**RESULTS.** COPM scores changed significantly over time in both groups ( $p = .03$ ). The change in Satisfaction scores showed a significant difference in favor only of APSM (effect size = 0.74 [0.11, 1.4]). CIS scores decreased significantly in the experimental group only ( $p < .01$ ).

**CONCLUSION.** APSM was found to be feasible and effective in optimizing participation in desired daily life activities in women with CFS. Replication in a larger sample with long-term follow-up is required.

## Original Article

# A prospective, proof-of-concept investigation of KPAX002 in chronic fatigue syndrome

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**Abstract:** Stimulant drugs and various micronutrient interventions have previously been studied in chronic fatigue syndrome (CFS) but they have never been studied in combination. This proof of concept investigation seeks to examine the clinical effects and safety profile of KPAX002 (a combination of methylphenidate hydrochloride and mitochondrial support nutrients) in patients with CFS. Fifteen patients diagnosed with CFS by 1994 Fukuda criteria were recruited and treated with KPAX002 to explore a potential synergistic effect of this combination. Fatigue and concentration disturbance symptoms were measured at baseline, 4 weeks, and 12 weeks using two clinically validated tools: Checklist Individual Strength (CIS) and Visual Analog Scale (VAS). The primary outcome objective was a decrease in the total CIS score of  $\geq 25\%$  in at least 50% of the subjects. The mean total CIS score decreased by 36.4 points (34%) at 12 weeks ( $P < 0.0001$ ), corresponding to a  $\geq 25\%$  decrease in 87% of the participants. Treatment with KPAX002 was well tolerated and significantly improved fatigue and concentration disturbance symptoms in greater than 50% of patients with CFS. These results were statistically significant. This combination treatment is worthy of additional investigation.

## **Low NK Cell Activity in Chronic Fatigue Syndrome (CFS) and Relationship to Symptom Severity**

David Strayer, Victoria Scott and William Carter

### **Abstract**

*Background:* Natural killer (NK) cells act as an immune surveillance against invading pathogens and tumors. NK cell cytotoxicity (NKCC) has been reported to be decreased in patients with CFS.

**Methods:** The objective of this review was to conduct an analysis of available publications that reported NKCC data in CFS in order to evaluate any relationships to case definitions used to define CFS and symptom severity.

**Results:** Of 17 studies that evaluated NKCC in patients with CFS, defined using the CDC 1988 and/or 1994 case definition (CD), 88% (15/17) concluded that NKCC was decreased in CFS patients compared to normal controls. The NKCC decrease was seen using two established methods, <sup>51</sup>Cr release (11/13) and flow cytometry (4/4). The mean percent decrease in NKCC using the CDC 1988 CD (66.3%) was significantly greater than that using the CDC 1994 CD (49.7%) ( $p < 0.01$ ).

This result is consistent with that of six publications showing a greater decrease in NKCC associated with increased CFS symptom severity based on the lower symptom requirement for the CDC 1994 vs. 1988 CD. In contrast, there was no significant difference in the mean percent decrease in NKCC seen comparing the CDC 1994 CD defined population using the <sup>51</sup>Cr release (48.3%) vs. flow cytometry (50.7%) assays ( $p > 0.5$ ).

Finally, seven studies investigating the ability of various agents to augment NKCC in patients with CFS showed increases of NKCC with both in vitro exposure (4/5) and in vivo exposure using randomized trials (2/2).

**Conclusions:** Low NKCC is commonly seen in CFS and is associated with increase symptom severity.

<http://www.ncbi.nlm.nih.gov/pubmed/26354426>

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### **HPV vaccination syndrome. A questionnaire-based study.**

Martínez-Lavín M, Martínez-Martínez LA, Reyes-Loyola P.

#### ***Abstract***

Isolated cases and small series have described the development of complex regional pain syndrome, postural orthostatic tachycardia, and fibromyalgia after human papillomavirus (HPV) vaccination. These illnesses are difficult to diagnose and have overlapping clinical features.

Small fiber neuropathy and dysautonomia may play a major role in the pathogenesis of these entities. We used the following validated questionnaires to appraise the chronic illness that might appear after HPV vaccination: The 2010 American College of Rheumatology Fibromyalgia Diagnostic Criteria, COMPASS 31 dysautonomia questionnaire, and S-LANSS neuropathic pain form.

These questionnaires and a "present illness" survey were e-mailed to persons who had the onset of a chronic ailment soon after HPV vaccination. Forty-five filled questionnaires from individuals living in 13 different countries were collected in a month's period. Mean ( $\pm$ SD) age at vaccination time was  $14 \pm 5$  years. Twenty-nine percent of the cases had immediate (within 24 h) post-vaccination illness onset. The most common presenting complaints were musculoskeletal pain (66 %), fatigue (57 %), headache (57 %), dizziness/vertigo (43 %), and paresthesias/allodynia (36 %).

Fifty-three percent of affected individuals fulfill the fibromyalgia criteria. COMPASS-31 score was  $43 \pm 21$ , implying advanced autonomic dysfunction. Eighty-three percent of the patients who had ongoing pain displayed S-LANSS values  $>12$ , suggesting a neuropathic component in their pain experience.

After a mean period of  $4.2 \pm 2.5$  years post-vaccination, 93 % of patients continue to have incapacitating symptoms and remain unable to attend school or work.

In conclusion, a disabling syndrome of chronic neuropathic pain, fatigue, and autonomic dysfunction may appear after HPV vaccination.

**Capturing the post-exertional exacerbation of fatigue following physical and cognitive challenge in patients with chronic fatigue syndrome.**

Keech A1, Sandler CX2, Vollmer-Conna U3, Cvejic E3, Lloyd AR4, Barry BK5.

**Abstract**

**OBJECTIVE:** To design and validate an instrument to capture the characteristic post-exertional exacerbation of fatigue in patients with chronic fatigue syndrome (CFS).

**METHODS:** Firstly, patients with CFS (N=19) participated in five focus group discussions to jointly explore the nature of fatigue and dynamic changes after activity, and inform development of a self-report instrument - the Fatigue and Energy Scale (FES). The psychometric properties of the FES were then examined in two case-control challenge studies: a physically-demanding challenge (moderate-intensity aerobic exercise; N=10 patients), and a cognitively-demanding challenge (simulated driving; N=11 patients). Finally, ecological validity was evaluated by recording in association with tasks of daily living (N=9).

**RESULTS:** Common descriptors for fatigue included 'exhaustion', 'tiredness', 'drained of energy', 'heaviness in the limbs', and 'foggy in the head'. Based on the qualitative data, fatigue was conceptualised as consisting of 'physical' and 'cognitive' dimensions.

Analysis of the psychometric properties of the FES showed good sensitivity to the changing symptoms during a post-exertional exacerbation of fatigue following both physical exercise and driving simulation challenges, as well as tasks of daily living.

**CONCLUSION:** The 'fatigue' experienced by patients with CFS covers both physical and cognitive components. The FES captured the phenomenon of a post-exertional exacerbation of fatigue commonly reported by patients with CFS. The characteristics of the symptom response to physical and cognitive challenges were similar. Both the FES and the challenge paradigms offer key tools to reliably investigate biological correlates of the dynamic changes in fatigue.

**Brain White Matter Abnormalities in Female Interstitial Cystitis/Bladder Pain Syndrome: A MAPP Network Neuroimaging Study.**

Farmer MA1, Huang L, Martucci K, Yang CC, Maravilla KR, Harris RE, Clauw DJ, Mackey S, Ellingson BM, Mayer EA, Schaeffer AJ, Apkarian AV; MAPP Research Network.

**Abstract**

**PURPOSE:** Several chronic pain conditions may be distinguished by condition specific brain anatomical and functional abnormalities on imaging, which are suggestive of underlying disease processes. We present what is to our knowledge the first characterization of interstitial cystitis/bladder pain syndrome associated white matter (axonal) abnormalities based on multicenter neuroimaging from the MAPP Research Network.

**MATERIALS AND METHODS:** We assessed 34 women with interstitial cystitis/bladder pain syndrome and 32 healthy controls using questionnaires on pain, mood and daily function. White matter microstructure was evaluated by diffusion tensor imaging to model directional water flow along axons or fractional anisotropy. Regions correlating with clinical parameters were further examined for gender and syndrome dependence.

**RESULTS:** Women with interstitial cystitis/bladder pain syndrome showed numerous white matter abnormalities that correlated with pain severity, urinary symptoms and impaired quality of life. Interstitial cystitis/bladder pain syndrome was characterized by decreased fractional anisotropy in aspects of the right anterior thalamic radiation, the left forceps major and the right longitudinal fasciculus. Increased fractional anisotropy was detected in the right superior and bilateral inferior longitudinal fasciculi.

**CONCLUSIONS:** To our knowledge we report the first characterization of brain white matter abnormalities in women with interstitial cystitis/bladder pain syndrome. Regional decreases and increases in white matter integrity across multiple axonal tracts were associated with symptom severity. Given that white matter abnormalities closely correlated with hallmark symptoms of interstitial cystitis/bladder pain syndrome, including bladder pain and urinary symptoms, brain anatomical alterations suggest that there are neuropathological contributions to chronic urological pelvic pain.



Eur J Pediatr. 2015 Sep 3. [Epub ahead of print]

**The impact of chronic fatigue syndrome on cognitive functioning in adolescents.**

Nijhof LN, Nijhof SL, Bleijenberg G, Stellato RK, Kimpen JL, Pol HE, van de Putte EM.

**Abstract**

Chronic fatigue syndrome (CFS) is characterized by persistent fatigue and severe disability. Most adolescent patients report attention and concentration problems, with subsequent poor performance at school.

This study investigated the impact of CFS on intellectual capacity by (1) assessing discrepancies between current intelligence quotient (IQ) and school level and (2) exploring differences in current IQ and pre-CFS school performance, compared with healthy individuals. Current data was cross-sectionally gathered and compared with retrospective pre-CFS school performance data.

Fifty-nine CFS adolescents and 40 controls were evaluated on performance on age-appropriate intelligence tests and school level. Current IQ scores of CFS adolescents were lower than expected on the basis of their school level.

Furthermore, there was a difference in intelligence performance across time when current IQ scores were compared with pre-CFS cognitive achievement.

Healthy controls did not show any discrepancies.

**CONCLUSION:** According to their pre-CFS intelligence assessments, CFS patients started with appropriate secondary school levels at the age of 12. Our data suggest that CFS may be accompanied by a decline in general cognitive functioning.

Given the critical age for intellectual development, we recommend a timely diagnosis followed by appropriate treatment of CFS in adolescents. *What is Known:* • *Adolescent chronic fatigue syndrome (CFS) is a debilitating condition with major impact on social and intellectual development.* • *Most patients report concentration problems, with subsequent poor performance at school.*

Little is known about the influence of CFS on intellectual performances. *What is New:* • *IQ scores of CFS adolescents are lower than the IQ scores of healthy peers with an equivalent school level.* • *There is a decrease in intelligence performance across time when current IQ scores are compared with pre-CFS cognitive achievement.*

Healthy controls do not show any discrepancies between their current IQ, school level and previous cognitive functioning. This suggest that adolescent CFS may be accompanied by a decline in general cognitive functioning.

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J Pain. 2015 Aug 31. pii: S1526-5900(15)00838-X. doi: 10.1016/j.jpain.2015.08.004. [Epub ahead of print]

**Effect of Milnacipran Treatment on Ventricular Lactate in Fibromyalgia: A Randomized, Double-blind, Placebo-controlled Trial.**

Natelson BH1, Vu D2, Mao X3, Weiduschat N3, Togo F4, Lange G2, Blate M2, Kang G3, Coplan JD5, Shungu DC3.

**Abstract**

Milnacipran, a serotonin/norepinephrine reuptake inhibitor (SNRI), is FDA-approved for the treatment of fibromyalgia (FM). This report presents the results of a randomized, double-blind, placebo-controlled trial of milnacipran conducted to test the hypotheses that (a) similar to patients with chronic fatigue syndrome, FM patients have elevated ventricular lactate at baseline; (b) 8 weeks of treatment with milnacipran will lower ventricular lactate levels compared to both baseline and to placebo; and (c) treatment with milnacipran will improve attention and executive function in the Attention Network Test compared to placebo.

In addition, we examined the results for potential associations between ventricular lactate and pain. Baseline ventricular lactate measured by proton magnetic resonance spectroscopic imaging (1H MRSI) was found to be higher in FM than in healthy controls [ $F(1,37) = 22.11$ ;  $p < 0.0001$ , partial  $\eta^2 = 0.37$ ].

Milnacipran reduced pain in FM relative to placebo but had no effect on cognitive processing. At study end, ventricular lactate in the milnacipran-treated group decreased significantly compared to baseline and to placebo [ $F(1,18) = 8.18$ ,  $p = 0.01$ , partial  $\eta^2 = 0.31$ ].

A significantly larger proportion of milnacipran-treated patients showed decreases in both ventricular lactate and in pain than placebo [ $p = 0.03$ ]. These results suggest that 1H MRSI measurements of lactate may serve as a potential biomarker for therapeutic response in FM and that milnacipran may act, at least in part, by targeting the brain response to glial activation and neuroinflammation.

**PERSPECTIVE:** Patients treated with milnacipran showed decreases in both pain and ventricular lactate compared to those treated with placebo, but, even after treatment, levels of ventricular lactate remained higher than in controls. The hypothesized mechanism for these decreases is via drug-induced reductions of a central inflammatory state.

Brain Behav Immun. 2015 Sep 20. pii: S0889-1591(15)30020-9. doi: 10.1016/j.bbi.2015.09.013.

**Antibodies to  $\beta$  adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome.**

Loebel M, Grabowski P, Heidecke H, Bauer S, Hanitsch LG, Wittke K, Meisel C, Reinke P, Volk HD, Fluge Ø, Mella O, Scheibenbogen C.

**Abstract**

Infection-triggered disease onset, chronic immune activation and autonomic dysregulation in CFS point to an autoimmune disease directed against neurotransmitter receptors. Autoantibodies against G-protein coupled receptors were shown to play a pathogenic role in several autoimmune diseases.

Here, serum samples from a patient cohort from Berlin (n= 268) and from Bergen with pre- and post-treatment samples from 25 patients treated within the KTS-2 rituximab trial were analysed for IgG against human  $\alpha$  and  $\beta$  adrenergic, muscarinic (M) 1-5 acetylcholine, dopamine, serotonin, angiotensin, and endothelin receptors by ELISA and compared to a healthy control cohort (n=108).

Antibodies against  $\beta_2$ , M3 and M4 receptors were significantly elevated in CFS patients compared to controls. In contrast, levels of antibodies against  $\alpha$  adrenergic, dopamine, serotonin, angiotensin, and endothelin receptors were not different between patients and controls.

A high correlation was found between levels of autoantibodies and elevated IgG1-3 subclasses, but not with IgG4. Further patients with high  $\beta_2$  antibodies had significantly more frequently activated HLA-DR+ T cells and more frequently thyroperoxidase and anti-nuclear antibodies. In patients receiving rituximab maintenance treatment achieving prolonged B-cell depletion, elevated  $\beta_2$  and M4 receptor autoantibodies significantly declined in clinical responder, but not in non-responder.

We provide evidence that 29.5% of patients with CFS had elevated antibodies against one or more M acetylcholine and  $\beta$  adrenergic receptors which are potential biomarkers for response to B-cell depleting therapy.

The association of autoantibodies with immune markers suggests that they activate B and T cells expressing  $\beta$  adrenergic and M acetylcholine receptors. Dysregulation of acetylcholine and adrenergic signalling could also explain various clinical symptoms of CFS.

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**creased serum levels of lipopolysaccharide and antflagellin antibodies in patients with diarrhea-predominant irritable bowel syndrome**

A. Dlugosz, P. Nowak, M. D'Amato, G. Mohammadian Kermani, J. Nyström, S. Abdurahman and G. Lindberg

**Abstract**

**Background:** Innate immune responses to conserved microbial products such as lipopolysaccharide (LPS) and flagellin are likely important in microbial–host interactions and intestinal homeostasis. We hypothesized that bacterial translocation and activation of mucosal immunity against common microbial antigens might be involved in the development of irritable bowel syndrome (IBS). We therefore compared serum levels of LPS, soluble CD14 (sCD14), and flagellin antibodies between patients with different subtypes of IBS and healthy controls.

**Methods:** We analyzed serum obtained from 88 patients (74 females) aged 19(43)–73 years and 106 healthy volunteers (77 females) aged 19(38)–62 years. Diarrhea-predominant IBS (D-IBS) was present in 32 patients (36%), 23 patients (26%) had constipation-predominant IBS (C-IBS), and 33 patients (38%) had A-IBS. We used ELISA for sCD14 and antflagellin immunoglobulin G and limulus amebocyte assay for LPS. Abdominal symptoms and psychiatric comorbidities were assessed using validated questionnaires.

**Key Results:** We found a significantly higher serum level of LPS in patients with D-IBS compared to controls ( $p = 0.0155$ ). The level of antibodies to flagellin was higher in patients with IBS than in controls (mainly driven by higher levels in D-IBS,  $p = 0.0018$ ). The levels of sCD14 were lower in D-IBS patients compared to controls ( $p = 0.0498$ ). We found a weak, but significant correlation between the levels of antflagellin antibodies and anxiety among IBS patients ( $\rho = 0.38$ ;  $p = 0.0045$ ).

**Conclusions & Inferences:** Our results support the concept that immune reactivity to luminal antigens may have a role in the development of D-IBS. The serum level of antflagellin antibodies was found to correlate with patients' self-reported anxiety score.

## **Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME): Characteristics of Responders to Rintatolimod**

David R Strayer, Bruce C Stouch, Staci R Stevens, Lucinda Bateman, Charles W Lapp, Daniel L Peterson, William A Carter, William M Mitchell

### **Abstract**

**Background:** Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a debilitating disease of unknown pathogenesis consisting of a variety of flu-like symptoms including severe fatigue. Initial analysis of the use of rintatolimod (Poly I: Poly C12U), a selective TLR3 agonist, in a Phase III, double-blind, randomized, placebo-controlled trial of CFS/ME demonstrated statistical significance ( $p < 0.05$ ) in the reduction of fatigue as measured by exercise tolerance (ET) as the primary endpoint using a modified Bruce protocol with reduced physical exertion in patients with severe CFS/ME as defined by a Karnofsky performance score (KPS) of 40-60.

**Methods and Findings:** In order to better identify responders to rintatolimod, primary and secondary endpoints have been reexamined post hoc as a function of a pre-specified study baseline ET duration  $>9$  minutes. Analysis of improvement in exercise performance at the  $\geq 25\%$  and  $\geq 50\%$  levels using ET at 40 weeks compared to baseline was performed for the intent-to-treat (ITT) population ( $n=208$ ) using the pre-specified baseline exercise stratum (baseline ET duration  $>9$  minutes).

For this subset of patients ( $n=126$ ), 33% ( $n=20$ ), and 12% ( $n=8$ ) of rintatolimod vs. placebo patients, respectively, improved ET duration by  $\geq 25\%$  ( $p=0.004$ ) while 23% ( $n=14$ ) compared to 4.5% ( $n=3$ ) of rintatolimod vs. placebo patients, respectively improved ET duration by  $\geq 50\%$  ( $p=0.003$ ). This corresponds to increases of  $\geq 186$  and  $\geq 373$  seconds for patients receiving rintatolimod, respectively, at  $\geq 25\%$  and  $\geq 50\%$  improvement responses.

A frequency distribution analysis of  $\geq 25\%$  improvement,  $<25\%$  change, and  $\geq 25\%$  deterioration in ET from baseline at 40 weeks for the baseline  $>9$  minutes cohort showed net improvement to be 18.3% for the rintatolimod cohort vs. 4.6% deterioration for placebo ( $p=0.015$ ). A continuous responder analysis using 5% increments from  $\geq 25\%$  to  $\geq 50\%$  provided a robust clinical enhancement in ET effect in the rintatolimod cohorts as compared to placebo.

The KPS and Vitality (SF-36 subscale) quality of life secondary endpoints demonstrated similar clinically significant improvements for the rintatolimod cohort as a function of the same ET dichotomization. Rintatolimod was generally well-tolerated in this CFS/ME population.

**Conclusions:** Using a modified Bruce ET protocol with reduced physical exertion allowed clear identification of patient responders to rintatolimod with severe CFS/ME syndrome. Rintatolimod produced significant enhancement in ET and quality of life indicators in patients able to complete  $>9$  minutes in a modified Bruce ET test.

Rintatolimod also reduced deterioration in ET compared to placebo in patients with the poorest initial ET. Exercise endurance  $>9$  minutes in a Bruce protocol modified for patients with CFS/ME provides a method to identify patients most likely to respond to rintatolimod.

## **Longitudinal analysis of immune abnormalities in varying severities of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis patients**

Sharni Lee Hardcastle\*, Ekua Weba Brenu, Samantha Johnston, Thao Nguyen, Teilah Huth, Sandra Ramos, Donald Staines and Sonya Marshall-Gradisnik

### **Abstract**

**Background:** Research has identified immunological abnormalities in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), a heterogeneous illness with an unknown cause and absence of diagnostic test. There have been no CFS/ME studies examining innate and adaptive immune cells longitudinally in patients with varying severities. This is the first study to investigate immune cells over 6 months while also examining CFS/ME patients of varying symptom severity.

**Methods:** Participants were grouped into 18 healthy controls, 12 moderate and 12 severe CFS/ME patients and flow cytometry was used to examine cell parameters at 0 and 6 months.

**Results:** Over time, iNKT CD62L expression significantly increased in moderate CFS/ME patients and CD56bright NK receptors differed in severe CFS/ME. Naïve CD8+T cells, CD8-CD4- and CD56-CD16- iNKT phenotypes,  $\gamma\delta$ 2T cells and effector memory subsets were significantly increased in severe CFS/ME patients at 6 months. Severe CFS/ME patients were significantly reduced in CD56brightCD16dim NKG2D, CD56dimCD16- KIR2DL2/DL3, CD94-CD11a-  $\gamma\delta$ 1T cells and CD62L+CD11a-  $\gamma\delta$ 1T cells at 6 months.

**Conclusions:** Severe CFS/ME patients differed from controls and moderate CFS/ME patients over time and expressed significant alterations in iNKT cell phenotypes, CD8+T cell markers, NK cell receptors and  $\gamma\delta$ T cells at 6 months. This highlights the importance of further assessing these potential immune biomarkers longitudinally in both moderate and severe CFS/ME patients.

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

1. Holton, K, Taren D, Thomson C, Bennett R, Jones K. The effect of dietary glutamate on fibromyalgia and irritable bowel symptoms. Clin and Exper Rheumatology. 2012 Vol 30 No. 6. Suppl 74.

*A key neurotransmitter in central sensitization is glutamate; which is the most ubiquitous excitatory neurotransmitter in mammals. In animal models, experimentally high glutamate levels have been shown to overexcite a neuron to the point of death."*<sup>1</sup>

Research shows a relationship between consumption of dietary glutamate and increased symptoms of fibromyalgia (FM) and irritable bowel syndrome (IBS). Study subjects maintained a daily symptom checklist throughout a four-week diet and two-week double-blind placebo-controlled crossover challenge. Significant decreases in symptoms were seen in participants who received the placebo rather than the dietary glutamate.

Fifty-seven people diagnosed with both FM and IBS participated in a 4-week diet that omitted dietary additive excitotoxins, including monosodium glutamate (MSG) and aspartame. The subjects received a group diet training session prior to the study and had access to professional dietary counseling throughout the study. They also maintained food/symptom journals during weeks one and four, and also Monday through Wednesday of the second part of the study.

Thirty-seven people completed the four-week diet and were eligible for the next portion of the study. Of those patients, 84% reported more than 30% of their symptoms were resolved. Eight participants reported fewer than 12 symptoms by the end of the four-week diet and on average 11 symptoms remitted in the subjects.

The second part of the study included a double-blind placebo-controlled challenge with MSG. The subjects received MSG or placebo for three consecutive days each week. Each subject tracked their symptoms daily on a checklist, which consisted of 28 symptoms of FM, IBS, and four 'Chinese Restaurant Syndrome' symptoms. All fibromyalgia symptoms were reported more frequently during the MSG challenge in the second part of the study. Severe fatigue was reported by 70 percent of the participants receiving MSG while only 30 percent of those receiving the placebo reported this side effect. All IBS symptoms were reported more frequently during the MSG challenge, except for straining during BM which remained the same as reported by 30 percent of the subjects. Significant differences were seen in abdominal pain and diarrhea between the MSG and non-MSG groups. Only 9% of those receiving the placebo reported these symptoms, while 32% of MSG recipients reported abdominal pain and diarrhea.

*Conclusion:* Patients whose symptoms improved during the (first part of the study) four-week diet saw the symptoms return when they received MSG in the second part of the study. Clinically significant symptom improvement was reported by 84% of the participants who completed the four-week diet and suggests a diet free of excitotoxin is not only feasible for individuals, but that it improves symptoms of FM/IBS. This indicates excitotoxins may evoke symptoms in some FM/IBS patients.

1. Holton, K, Taren D, Thomson C, Bennett R, Jones K. The effect of dietary glutamate on fibromyalgia and irritable bowel symptoms. Clin and Exper Rheumatology. 2012 Vol 30 No. 6. Suppl 74.

# Brain White Matter Abnormalities in Female Interstitial Cystitis/Bladder Pain Syndrome: A MAPP Network Neuroimaging Study.

[Farmer MA](#)<sup>1</sup>, [Huang L](#)<sup>1</sup>, [Martucci K](#)<sup>2</sup>, [Yang CC](#)<sup>3</sup>, [Maravilla KR](#)<sup>4</sup>, [Harris RE](#)<sup>5</sup>, [Clauw DJ](#)<sup>5</sup>, [Mackey S](#)<sup>2</sup>, [Ellingson BM](#)<sup>6</sup>, [Mayer EA](#)<sup>6</sup>, [Schaeffer AJ](#)<sup>7</sup>, [Apkarian AV](#)<sup>8</sup>; [MAPP Research Network](#).

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## Abstract

### **PURPOSE:**

Several chronic pain conditions may be distinguished by condition specific brain anatomical and functional abnormalities on imaging, which are suggestive of underlying disease processes. We present what is to our knowledge the first characterization of interstitial cystitis/bladder pain syndrome associated white matter (axonal) abnormalities based on multicenter neuroimaging from the MAPP Research Network.

### **MATERIALS AND METHODS:**

We assessed 34 women with interstitial cystitis/bladder pain syndrome and 32 healthy controls using questionnaires on pain, mood and daily function. White matter microstructure was evaluated by diffusion tensor imaging to model directional water flow along axons or fractional anisotropy. Regions correlating with clinical parameters were further examined for gender and syndrome dependence.

### **RESULTS:**

Women with interstitial cystitis/bladder pain syndrome showed numerous white matter abnormalities that correlated with pain severity, urinary symptoms and impaired quality of life. Interstitial cystitis/bladder pain syndrome was characterized by decreased fractional anisotropy in aspects of the right anterior thalamic radiation, the left forceps major and the right longitudinal fasciculus. Increased fractional anisotropy was detected in the right superior and bilateral inferior longitudinal fasciculi.

### **CONCLUSIONS:**

To our knowledge we report the first characterization of brain white matter abnormalities in women with interstitial cystitis/bladder pain syndrome. Regional decreases and increases in white matter integrity across multiple axonal tracts were associated with symptom severity. Given that white matter abnormalities closely correlated with hallmark symptoms of interstitial cystitis/bladder pain syndrome, including bladder pain and urinary symptoms, brain anatomical alterations suggest that there are neuropathological contributions to chronic urological pelvic pain.

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# Sleep Medicine

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## The effect of sleep deprivation on pain perception in healthy subjects: a meta-analysis

[Marlene Schrimpf](#),

[Gregor Liegl](#),

[Markus Boeckle](#),

[Anton Leitner](#),

[Peter Geisler](#),

[Christoph Pieh](#)

SMD<sub>Dp</sub> = 0.62 (Moderate Evidence)

## Highlights

- Sleep deprivation has a medium effect (SMD=0.62) on pain perception.
- The calculated effect-size is comparable with effect-sizes achieved through pain treatment.
- Sleep deprivation affects self-reported pain as well as pain threshold.

## Abstract

### Background

There is strong evidence indicating an interaction between sleep and pain. However, the size of this effect, as well as the clinical relevance is unclear. This meta-analysis was therefore conducted to quantify the effect of sleep deprivation on pain perception.

### Methods

A systematic literature search was conducted using the electronic databases PubMed, Cochrane, Psycinfo and Scopus. By conducting a random effect model, we calculated the pooled standardized mean differences (SMDs) of sleep deprivation on pain perception. Studies that investigated any kind of sleep deprivation in conjunction with a pain measurement were included. In cases of several pain measurements within a study, we calculated the average effect size of all measures.

### Results

We identified five eligible studies (N=190) for the between-group analysis and 10 studies (N=266) for the within-group analysis. Sleep deprivation showed a medium effect in the between group analysis (SMD=0.62; CI95: 0.12, 1.12; z=2.43; p=.015) and a large effect in the within-group analysis (SMD=1.49; CI95: 0.82, 2.17; z=4.35; p<.0001). The test for heterogeneity was not significant in the between-group analysis (Q=5.29; df=4; p=.2584), but was significant in the within-group analysis (Q=53.49; df=9; p<.0001).

### Conclusion

This meta-analysis confirms a medium effect (SMD=0.62) of sleep deprivation on pain perception. As this meta-analysis is based on experimental studies in healthy subjects, the clinical relevance should be clarified.

### Keywords:

[sleep deprivation](#), [pain perception](#), [meta-analysis](#), [reciprocal relation](#)

## Long-Term Outcome of the Management of Chronic Neuropathic Pain: A Prospective Observational Study

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### Abstract

This prospective observational cohort study addressed the long-term clinical effectiveness of the management of chronic neuropathic noncancer pain at 7 Canadian tertiary pain centers. Patients were treated according to standard guidelines and were followed at 3, 6, 12, 18, and 24 months. Standard outcome measures for pain, mood, quality of life, and overall treatment satisfaction were administered, with the primary outcome measure designated as the composite of 30% reduction in average pain intensity and 1-point decrease in the mean Interference Scale Score (0–10) of the Brief Pain Inventory at 12 months relative to baseline. Of 789 patients recruited, mean age was  $53.5 \pm 14.2$  years (55% female) and mean duration of pain was  $4.88 \pm 5.82$  years. Mean average pain intensity (0–10) at baseline was  $6.1 \pm 1.9$ . All standard outcome measures showed statistically significant improvement at 12 months relative to baseline ( $P < .001$ ). However, only 23.7% attained clinically significant improvement in pain and function at 12 months as the primary outcome measure. Univariable analyses showed poorer outcomes at 12-month follow-up with longer duration of pain ( $P = .002$ ), greater cigarette use ( $P = .01$ ), more disability compensation ( $P = .001$ ), and higher opioid doses at baseline and at 12 months ( $P < .02$ ). Our present treatment modalities provide significant long-term benefit in only about a quarter of patients with neuropathic pain managed at tertiary care pain clinics. Opioid therapy may not be beneficial for the long term.

### Perspective

Evidence-based treatment of chronic neuropathic pain provides long-term benefit in only about one-quarter of patients seen in tertiary care centers. Opioid therapy may not be beneficial

## Sleep and pain sensitivity in adults

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### Abstract

Abstract: Sleep problems and pain are major public health concerns, but the nature of the association between the 2 conditions is inadequately studied. The aim of this study was to determine whether a range of sleep measures is associated with experimental increased pain sensitivity. A cross-sectional large population-based study from 2007 to 2008, the Tromsø 6 study, provided data from 10,412 participants (age: mean [SD], 58 [13] years; 54% women). Self-reported sleep measures provided information on sleep duration, sleep onset latency (SOL), and sleep efficiency, as well as frequency and severity of insomnia. The main outcome measure was pain sensitivity tests, including assessment of cold-pressor pain tolerance. We found that all sleep parameters, except sleep duration, were significantly associated with reduced pain tolerance. Both the frequency and severity of insomnia, in addition to SOL and sleep efficiency, were associated with pain sensitivity in a dose–response manner. Adjusting for demographics and psychological distress reduced the strengths of the hazard ratios, but most associations remained significant in the fully adjusted models. There was also a synergistic interaction effect on pain tolerance when combining insomnia and chronic pain. We conclude that sleep problems significantly increase the risk for reduced pain tolerance. Because comorbid sleep problems and pain have been linked to elevated disability, the need to improve sleep among patients with chronic pain, and vice versa, should be an important agenda for future research.

<http://www.ncbi.nlm.nih.gov/pubmed/26429318>

Hum Immunol. 2015 Sep 28. pii: S0198-8859(15)00465-6. doi: 10.1016/j.humimm.2015.09.028. [Epub ahead of print]

### **Frequent IgG subclass and mannose binding lectin deficiency in patients with Chronic Fatigue Syndrome.**

Guenther S, Loebel M, Mooslechner AA, Knops M, Hanitsch LG, Grabowski P, Wittke K, Meisel C, Unterwalder N, Volk HD, Scheibenbogen C.

#### **Abstract**

Chronic fatigue syndrome (CFS) is a severe disease characterized by various symptoms of immune dysfunction. CFS onset is typically with an infection and many patients suffer from frequently recurrent viral or bacterial infections. Immunoglobulin and mannose binding lectin (MBL) deficiency are frequent causes for increased susceptibility to infections.

In this study we retrospectively analysed 300 patients with CFS for immunoglobulin and MBL levels, and B-cell subset frequencies. 25% of the CFS patients had decreased serum levels of at least one antibody class or subclass with IgG3 and IgG4 subclass deficiencies as most common phenotypes. However, we found elevated immunoglobulin levels with an excess of IgM and IgG2 in particular in another 25% of patients.

No major alteration in numbers of B cells and B-cell subsets was seen. Deficiency of MBL was found in 15% of the CFS patients in contrast to 6% in a historical control group. In a 2nd cohort of 168 patients similar frequencies of IgG subclass and MBL deficiency were found.

Thus, humoral immune defects are frequent in CFS patients and are associated with infections of the respiratory tract.

## **Autonomic function in chronic fatigue syndrome with and without painful temporomandibular disorder**

Lucy J. Robinson, Justin Durham, Laura L. MacLachlan & Julia L. Newton

### **Abstract**

**Background:** Chronic fatigue syndrome (CFS) is heterogeneous in nature, yet no clear subclassifications currently exist. There is evidence of dysautonomia in almost 90% of patients and CFS is often co-morbid with conditions associated with autonomic nervous system (ANS) dysfunction, such as temporomandibular disorders (TMD). The present study examined the point prevalence of TMD in a sample of people with CFS and explored whether co-morbidity between the conditions is associated with greater ANS dysfunction than CFS alone.

**Method:** Fifty-one patients and 10 controls underwent screening for TMD. They completed a self-report measure of ANS function (COMPASS-31) and objective assessment of heart rate variability during rest and standing (derived using spectral analysis). Frequency densities in the high-frequency (HF) and low-frequency (LF) band were calculated.

**Results:** Patients with CFS were divided into those who screened positive for TMD ( $n = 16$ , 31%; CFS + TMD) and those who did not ( $n = 35$ , 69%; CFS – TMD). Both CFS groups had significantly higher self-rated ANS dysfunction than controls. CFS + TMD scored higher than CFS – TMD on the orthostatic and vasomotor subscales. The CFS + TMD group had significantly higher HF and significantly lower LF at rest than the other two groups. In discriminant function analysis, self-report orthostatic intolerance and HF units correctly classified 75% of participants.

**Conclusions:** Almost one-third of CFS patients screened positive for TMD and this was associated with greater evidence of parasympathetic dysfunction. The presence of TMD shows potential as an effective screen for patients with CFS showing an autonomic profile and could help identify subgroups to target for treatment.

Trials. 2015 Oct 5;16(1):439. doi: 10.1186/s13063-015-0971-z.

## **Cytokine inhibition in chronic fatigue syndrome patients: study protocol for a randomized controlled trial.**

Roerink ME, Knoop H, Bredie SJ, Heijnen M, Joosten LA, Netea MG, Dinarello CA, van der Meer JW.

### **Abstract**

**BACKGROUND:** Chronic fatigue syndrome (CFS) is a medically unexplained syndrome for which no somatic or pharmacological treatment has been proven effective. Dysfunction of the cytokine network has been suspected to play a role in the pathophysiology of CFS. The disturbances of the cytokine network detected in CFS patients are highly variable, in part due to the lack of adequate controls in many studies. Furthermore, all studies have been performed on peripheral venous blood of patients. As cytokines mainly act in tissues, for example, the brain, the information that can be derived from peripheral blood cells is limited. The information regarding the possible role of cytokines in the pathophysiology could come from intervention studies in which the activities of relevant cytokines are reduced, for example, reducing interleukin-1, interleukin-6 or tumor necrosis factor. In this study, the clinical usefulness of anakinra, an IL-1 antagonist, will be assessed in patients with CFS.

**METHODS/DESIGN:** A randomized placebo-controlled, double-blind trial will be conducted. Fifty adult female patients meeting the Centers for Disease Control (CDC) criteria for CFS and without psychiatric co-morbidity will be included. After inclusion, patients will be randomized between treatment with anakinra (recombinant human interleukin-1 receptor antagonist) or placebo. Each group will be treated for 4 weeks. Outcome measures will be assessed at baseline, after 4 weeks of intervention, and 6 months after baseline assessment. The primary outcome measure will be fatigue severity at 4 weeks, measured with the validated Checklist of Individual Strength (CIS). Secondary outcome measures are functional impairment, physical and social functioning, psychological distress, pain severity, presence of accompanying symptoms, and cytokine and cortisol concentrations.

**DISCUSSION:** This is the first randomized placebo-controlled trial that will evaluate the effect of interference with IL-1 on the experience of fatigue in patients with CFS. The results of this study may expand treatment options for patients with CFS, for whom graded exercise therapy and cognitive behavioral therapy are the only evidence-based interventions that exist at this moment.

**TRIAL REGISTRATION:** Clinicaltrials.gov: NCT02108210 .Clinicaltrials.gov registration date: 8 April 2014. EudraCT: 2013-005466-19.

PMID:26438161 [PubMed - in process]

Pain Physician. 2015 Sep-Oct;18(5):E841-E852.

**Associations Between Cognitive Performance and Pain in Chronic Fatigue Syndrome: Comorbidity with Fibromyalgia Does Matter.**

Ickmans K, Meeus M, De Kooning M, Lambrecht L, Pattyn N, Nijs J.

**Abstract**

**BACKGROUND:** In addition to the frequently reported pain complaints, performance-based cognitive capabilities in patients with chronic fatigue syndrome (CFS) with and without comorbid fibromyalgia (FM) are significantly worse than those of healthy controls. In various chronic pain populations, cognitive impairments are known to be related to pain severity. However, to the best of our knowledge, the association between cognitive performance and experimental pain measurements has never been examined in CFS patients.

**OBJECTIVES:** This study aimed to examine the association between cognitive performance and self-reported as well as experimental pain measurements in CFS patients with and without FM.

**STUDY DESIGN:** Observational study.

**SETTING:** The present study took place at the Vrije Universiteit Brussel and the University of Antwerp.

**METHODS:** Forty-eight (18 CFS-only and 30 CFS+FM) patients and 30 healthy controls were studied. Participants first completed 3 performance-based cognitive tests designed to assess selective and sustained attention, cognitive inhibition, and working memory capacity. Seven days later, experimental pain measurements (pressure pain thresholds [PPT], temporal summation [TS], and conditioned pain modulation [CPM]) took place and participants were asked to fill out 3 questionnaires to assess self-reported pain, fatigue, and depressive symptoms.

**RESULTS:** In the CFS+FM group, the capacity of pain inhibition was significantly associated with cognitive inhibition. Self-reported pain was significantly associated with simple reaction time in CFS-only patients. The CFS+FM but not the CFS-only group showed a significantly lower PPT and enhanced TS compared with controls.

**LIMITATIONS:** The cross-sectional nature of this study does not allow for inferences of causation.

**CONCLUSIONS:** The results underline disease heterogeneity in CFS by indicating that a measure of endogenous pain inhibition might be a significant predictor of cognitive functioning in CFS patients with FM, while self-reported pain appears more appropriate to predict cognitive functioning in CFS patients without FM.

PMID:26431138 [PubMed - as supplied by publisher]

## **Recent Research on Gulf War illness and other health problems in veterans of the 1991 Gulf War: Effects of toxicant exposures during deployment**

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### Abstract

Veterans of the 1991 Gulf War (GW) are a unique population of veterans who returned from theatre with multiple health complaints and disorders. Studies in the U.S. and elsewhere have consistently concluded that approximately 25-32% of this population suffers from a disorder characterized by symptoms that vary somewhat among individuals and include fatigue, headaches, cognitive dysfunction, musculoskeletal pain, and respiratory, gastrointestinal and dermatologic complaints. Gulf War illness (GWI) is the term used to describe this disorder. In addition, brain cancer occurs at increased rates in subgroups of GW veterans, as do neuropsychological and brain imaging abnormalities.

Chemical exposures have become the focus of etiologic GWI research because nervous system symptoms are prominent and many neurotoxicants were present in theatre, including organophosphates, carbamates, and other pesticides; sarin/cyclosarin nerve agents, and pyridostigmine bromide (PB) medications used as prophylaxis against chemical warfare attacks. Psychiatric etiologies have been ruled out.

This paper reviews the recent literature on the health of 1991 GW veterans, focusing particularly on the central nervous system and on effects of toxicant exposures. In addition, it emphasizes research published since 2008, following on an exhaustive review that was published in that year that summarizes the prior literature (RACGWI, 2008).

We conclude that exposure to pesticides and/or to PB are causally associated with GWI and the neurological dysfunction in GW veterans.

Exposure to sarin and cyclosarin and to oil well fire emissions are also associated with neurologically based health effects, though their contribution to development of the disorder known as GWI is less clear. Gene-environment interactions are likely to have contributed to development of GWI in deployed veterans. The health consequences of chemical exposures in the GW and other conflicts have been called "toxic wounds" by veterans. This type of injury requires further study and concentrated treatment research efforts that may also benefit other occupational groups with similar exposure-related illnesses.



## **Mitochondrial Myopathy in Follow-up of a Patient With Chronic Fatigue Syndrome**

Fernando Galán, AOPT, Isabel de Laverá, PhD, David Cotán, PhD, José A. Sánchez-Alcázar, AOPT

Journal of Investigative Medicine High Impact Case Reports

### ***Abstract***

**Introduction.** Symptoms of mitochondrial diseases and chronic fatigue syndrome (CFS) frequently overlap and can easily be mistaken.

**Methods.** We report the case of a patient diagnosed with CFS and during follow-up was finally diagnosed with mitochondrial myopathy by histochemical study of muscle biopsy, spectrophotometric analysis of the complexes of the mitochondrial respiratory chain, and genetic studies.

**Results.** The results revealed 3% fiber-ragged blue and a severe deficiency of complexes I and IV and several mtDNA variants. Mother, sisters, and nephews showed similar symptoms, which strongly suggests a possible maternal inheritance. The patient and his family responded to treatment with high doses of riboflavin and thiamine with a remarkable and sustained fatigue and muscle symptoms improvement.

**Conclusions.** This case illustrates that initial symptoms of mitochondrial disease in adults can easily be mistaken with CFS, and in these patients a regular reassessment and monitoring of symptoms is recommended to reconfirm or change the diagnosis.

**A new case definition of Neuro-Inflammatory and Oxidative Fatigue (NIOF), a neuroprogressive disorder, formerly known as chronic fatigue syndrome or Myalgic Encephalomyelitis: results of multivariate pattern recognition methods and external validation by neuro-immune biomarkers.**

Maes M.

**Abstract**

**BACKGROUND:** Chronic fatigue syndrome (CFS) or Myalgic Encephalomyelitis (ME) is characterized by neuro-psychiatric (e.g. depression, irritability, sleep disorders, autonomic symptoms and neurocognitive defects) and physio-somatic (fatigue, a flu-like malaise, hyperalgesia, irritable bowel, muscle pain and tension) symptoms. New ME/CFS case definitions based on consensus criteria among experts are largely inadequate, e.g. those of the US Institute of Medicine .

**OBJECTIVES:** The aim of the present study was to delineate a new case definition of ME/CFS based on pattern recognition methods and using neuro-immune, inflammatory, oxidative and nitrosative stress (neuro-IO&NS) biomarkers as external validating criteria.

**METHODS:** We measured the 12-item Fibromyalgia and Chronic Fatigue Syndrome Rating (FF) Scale in 196 subjects with CFS (CDC criteria) and 83 with chronic fatigue. The "Neuro-IO&NS" biomarkers were: IgM / IgA responses against LPS of gut commensal bacteria (leaky gut), IgM responses to O&NS modified neoepitopes, autoimmunity to serotonin, plasma interleukin-1 (IL-1) and serum neopterin.

**RESULTS:** Cluster analysis showed the presence of two well-separated clusters with highly significant differences in symptoms and biomarkers. The cluster with higher scores on all FF items was externally validated against all IO&NS biomarkers and therefore this diagnostic group was labeled "Neuro-IO&NS Fatigue" or "Neuro-Inflammatory and Oxidative Fatigue" (NIOF).

An algorithm was constructed which defined NIOF as chronic fatigue and 4 or more of the following 6 symptoms: muscle tension, memory disturbances, sleep disorders, irritable bowel, headache or a flu-like malaise.

There was a significant overlap between NIOF and CFS although NIOF criteria were much more restrictive. Factor analysis showed two factors, the first a fatigue-hyperalgesia (fibromyalgic complaints) and the second a fatigue-depression factor.

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Brain Connect. 2015 Oct 9. [Epub ahead of print]

**Abnormal Resting-State Functional Connectivity in Patients with Chronic Fatigue Syndrome: Results of Seed and Data-Driven Analyses.**

Gay C, Robinson ME, Lai S, O'Shea A, Craggs J, Price DD, Staud R.

**Abstract**

Although altered resting-state functional connectivity is a characteristic of many chronic pain conditions it has not yet been evaluated in patients with chronic fatigue. Our objective was to investigate the association between fatigue and altered resting-state functional connectivity in myalgic-encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Thirty-six female subjects, 19 ME/CFS and 17 healthy controls completed a fatigue inventory before undergoing functional magnetic-resonance imaging. Two methods, 1) data driven and 2) model-based, were used to estimate and compare the intra-regional functional connectivity between both groups during the resting state (RS).

The first approach using independent-component analysis was applied to investigate five RS-networks: the default mode network (DMN), salience network (SN), left and right fronto-parietal networks (LFPN, RFPN), and sensory-motor network (SMN).

The second approach used a-priori selected seed regions demonstrating abnormal regional cerebral blood-flow (rCBF) in ME/CFS patients at rest.

In ME/CFS patients, Method-1 identified decreased intrinsic connectivity among regions within the LFPN. Furthermore, the functional connectivity of the left anterior mid-cingulate with the SMN and the connectivity of the left posterior-cingulate cortex with the SN were significantly decreased.

For Method-2, five distinct clusters within the right parahippocampus and occipital lobes, demonstrating significant rCBF reductions in ME/CFS patients were used as seeds.

The parahippocampal seed and three occipital-lobe seeds showed altered functional connectivity with other brain regions. The degree of abnormal connectivity correlated with the level of self-reported fatigue.

Our results confirm altered RS functional connectivity in patients with ME/CFS which was significantly correlated with the severity of their chronic fatigue.

# Early Menopause and Other Gynecologic Risk Indicators for Chronic Fatigue Syndrome in Women

Roumiana S. Boneva, MD, PhD; Jin-Mann S. Lin, PhD; Elizabeth R. Unger, PhD, MD  
| [Disclosures](#)

Menopause. 2015;22(8):826-834.

## *Abstract*

**Objective.** This study aims to examine whether gynecologic conditions are associated with chronic fatigue syndrome (CFS).

**Methods.** This study includes a subset of 157 women from a population-based case-control study in Georgia, United States, conducted in 2004-2009. Gynecologic history was collected using a self-administered questionnaire. Crude odds ratios (ORs) with 95% CIs and ORs adjusted for body mass index and other covariates, where relevant, were estimated for gynecologic conditions between 84 CFS cases and 73 healthy controls.

**Results.** Cases and controls were of similar age. Women with CFS reported significantly more gynecologic conditions and surgical operations than controls: menopause status (61.9% vs 37.0%; OR, 2.37; 95% CI, 1.21-4.66), earlier mean age at menopause onset (37.6 vs 48.6 y; adjusted OR, 1.22; 95% CI, 1.09-1.36), excessive menstrual bleeding (73.8% vs 42.5%; adjusted OR, 3.33; 95% CI, 1.66-6.70), bleeding between periods (48.8% vs 23.3%; adjusted OR, 3.31; 95% CI, 1.60-6.86), endometriosis (29.8% vs 12.3%; adjusted OR, 3.67; 95% CI, 1.53-8.84), use of noncontraceptive hormonal preparations (57.1% vs 26.0%; adjusted OR, 2.95; 95% CI, 1.36-6.38), nonmenstrual pelvic pain (26.2% vs 2.7%; adjusted OR, 11.98; 95% CI, 2.57-55.81), and gynecologic surgical operation (65.5% vs 31.5%; adjusted OR, 3.33; 95% CI, 1.66-6.67), especially hysterectomy (54.8% vs 19.2%; adjusted OR, 3.23; 95% CI, 1.46-7.17). Hysterectomy and oophorectomy occurred at a significantly younger mean age in the CFS group than in controls and occurred before CFS onset in 71% of women with records of date of surgical operation and date of CFS onset.

**Conclusions.** Menstrual abnormalities, endometriosis, pelvic pain, hysterectomy, and early/surgical menopause are all associated with CFS. Clinicians should be aware of the association between common gynecologic problems and CFS in women. Further work is warranted to determine whether these conditions contribute to the development and/or perpetuation of CFS in some women.

<http://www.scientificamerican.com/article/the-tantalizing-links-between-gut-microbes-and-the-brain/>

## The Tantalizing Links between Gut Microbes and the Brain

Neuroscientists are probing the idea that intestinal microbiota might influence brain development and behavior

By Peter Andrey Smith and Nature magazine | October 24, 2015

Nearly a year has passed since Rebecca Knickmeyer first met the participants in her latest study on brain development. Knickmeyer, a neuroscientist at the University of North Carolina School of Medicine in Chapel Hill, expects to see how 30 newborns have grown into crawling, inquisitive one-year-olds, using a battery of behavioural and temperament tests. In one test, a child's mother might disappear from the testing suite and then reappear with a stranger. Another ratchets up the weirdness with some Halloween masks. Then, if all goes well, the kids should nap peacefully as a noisy magnetic resonance imaging machine scans their brains.

“We try to be prepared for everything,” Knickmeyer says. “We know exactly what to do if kids make a break for the door.”

Knickmeyer is excited to see something else from the children—their faecal microbiota, the array of bacteria, viruses and other microbes that inhabit their guts. Her project (affectionately known as 'the poop study') is part of a [small but growing effort by neuroscientists](#) to see whether the microbes that colonize the gut in infancy can alter brain development.

The project comes at a crucial juncture. A growing body of data, mostly from animals raised in sterile, germ-free conditions, shows that microbes in the gut influence behaviour and can alter brain physiology and neurochemistry.

In humans, the data are more limited. Researchers have drawn links between gastrointestinal pathology and psychiatric neurological conditions such as anxiety, depression, autism, schizophrenia and neurodegenerative disorders—but they are just links.

“In general, the problem of causality in microbiome studies is substantial,” says Rob Knight, a microbiologist at the University of California, San Diego. “It's very difficult to tell if microbial differences you see associated with diseases are causes or consequences.” There are many outstanding questions. Clues about the mechanisms by which gut bacteria might interact with the brain are starting to emerge, but no one knows how important these processes are in human development and health.

# Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial

Prof [Michael Sharpe](#) [Kimberley A Goldsmith](#) Prof [Anthony L Johnson](#) Prof [Trudie Chalder](#) [Jane Walker](#) Prof [Peter D White](#)

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## Summary

### Background

The PACE trial found that, when added to specialist medical care (SMC), cognitive behavioural therapy (CBT), or graded exercise therapy (GET) were superior to adaptive pacing therapy (APT) or SMC alone in improving fatigue and physical functioning in people with chronic fatigue syndrome 1 year after randomisation. In this pre-specified follow-up study, we aimed to assess additional treatments received after the trial and investigate long-term outcomes (at least 2 years after randomisation) within and between original treatment groups in those originally included in the PACE trial.

### Methods

The PACE trial was a parallel-group randomised controlled trial of patients meeting Oxford criteria for chronic fatigue syndrome who were recruited from six secondary care clinics in the UK between March 18, 2005, and Nov 28, 2008. Participants were randomly allocated to receive SMC alone or plus APT, CBT, or GET. Primary outcomes (were fatigue measured with Chalder fatigue questionnaire score and physical functioning with short form-36 subscale score, assessed 1 year after randomisation. In this long-term follow-up, we sent postal questionnaires to assess treatment received after the trial and outcomes a minimum of 2 years after randomisation. We assessed long-term differences in outcomes within and between originally randomised groups. The PACE trial is registered at <http://isrctn.org>, number ISRCTN54285094.

### Findings

Between May 8, 2008, and April 26, 2011, 481 (75%) participants from the PACE trial returned questionnaires. Median time from randomisation to return of long-term follow-up assessment was 31 months (IQR 30–32; range 24–53). 210 (44%) participants received additional treatment (mostly CBT or GET) after the trial; with participants originally assigned to SMC alone (73 [63%] of 115) or APT (60 [50%] of 119) more likely to seek treatment than those originally assigned to GET (41 [32%] of 127) or CBT (36 [31%] of 118;  $p < 0.0001$ ). Improvements in fatigue and physical functioning reported by participants originally assigned to CBT and GET were maintained (within-group comparison of fatigue and physical functioning, respectively, at long-term follow-up as compared with 1 year: CBT  $-2.2$  [95% CI  $-3.7$  to  $-0.6$ ],  $3.3$  [0.02 to 6.7]; GET  $-1.3$  [ $-2.7$  to  $0.1$ ],  $0.5$  [ $-2.7$  to  $3.6$ ]). Participants allocated to APT and to SMC alone in the trial improved over the follow-up period compared with 1 year (fatigue and physical functioning, respectively: APT  $-3.0$  [ $-4.4$  to  $-1.6$ ],  $8.5$  [4.5 to 12.5]; SMC  $-3.9$  [ $-5.3$  to  $-2.6$ ],  $7.1$  [4.0 to 10.3]). There was little evidence of differences in outcomes between the randomised treatment groups at long-term follow-up.

### Interpretation

The beneficial effects of CBT and GET seen at 1 year were maintained at long-term follow-up a median of 2.5 years after randomisation. Outcomes with SMC alone or APT improved from the 1 year outcome and were similar to CBT and GET at long-term follow-up, but these data should be interpreted in the context of additional therapies having being given according to physician choice and patient preference after the 1 year trial final assessment. Future research should identify predictors of response to CBT and GET and also develop better treatments for those who respond to neither.

Sleep Science

## **Sleep quality and the treatment of intestinal microbiota imbalance in Chronic Fatigue Syndrome: A pilot study**

Melinda L. Jackson, Henry Butt, Michelle Ball, Donald Lewis, Dorothy Bruck

### **Abstract**

Chronic Fatigue Syndrome (CFS) is a multisystem illness, which may be associated with imbalances in gut microbiota. This study builds on recent evidence that sleep may be influenced by gut microbiota, by assessing whether changes to microbiota in a clinical population known to have both poor sleep and high rates of colonization with gram-positive faecal *Streptococcus*, can improve sleep.

Twenty-one CFS participants completed a 22- day open label trial. Faecal microbiota analysis was performed at baseline and at the end of the trial.

Participants were administered erythromycin 400 mg b.d. for 6 days. Actigraphy and questionnaires were used to monitor sleep, symptoms and mood. Changes in patients who showed a clinically significant change in faecal *Streptococcus* after treatment (responders; defined as post-therapy distribution <6%) were compared to participants who did not respond to treatment.

In the seven responders, there was a significant increase in actigraphic total sleep time ( $p=0.028$ ) from baseline to follow up, compared with non-responders. Improved vigour scores were associated with a lower *Streptococcus* count ( $\rho=-0.90$ ,  $p=0.037$ ). For both the responders and the whole group, poorer mood was associated with higher *Lactobacillus*.

Short term antibiotic treatment appears to be insufficient to effect sustainable changes in the gut ecosystem in most CFS participants. Some improvement in objective sleep parameters and mood were found in participants with reduced levels of gram-positive gut microbiota after antibiotic treatment, which is encouraging.

Further study of possible links between gut microorganisms and sleep and mood disturbances is warranted.

Int J Psychol Behav Sci. 2015;5(2):98-107.

### **A Cross Cultural Comparison of Disability and Symptomatology Associated with CFS.**

Zdunek M, Jason LA, Evans M, Jantke R, Newton JL

#### **Abstract**

Few studies have compared symptomatology and functional differences experienced by patients with chronic fatigue syndrome (CFS) across cultures. The current study compared patients with CFS from the United States (US) to those from the United Kingdom (UK) across areas of functioning, symptomatology, and illness onset characteristics.

Individuals in each sample met criteria for CFS as defined by Fukuda et al. (1994). These samples were compared on two measures of disability and impairment, the DePaul Symptom Questionnaire (DSQ) and the Medical outcomes study 36-item short-form health survey (SF-36).

Results revealed that the UK sample was significantly more impaired in terms of mental health and role emotional functioning, as well as specific symptoms of pain, neurocognitive difficulties, and immune manifestations. In addition, the UK sample was more likely to be working rather than on disability.

Individuals in the US sample reported more difficulties falling asleep, more frequently reported experiencing a sudden illness onset (within 24 hours), and more often reported that the cause of illness was primarily due to physical causes.

These findings suggest that there may be important differences in illness characteristics across individuals with CFS in the US and the UK, and this has implications for the comparability of research findings across these two countries.



Vaccine. 2015 Oct 13. pii: S0264-410X(15)01433-4. doi: 10.1016/j.vaccine.2015.10.018. [Epub ahead of print]

**Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine.**

Magnus P1, Gunnes N2, Tveito K3, Bakken IJ2, Ghaderi S2, Stoltenberg C2, Hornig M4, Lipkin WI4, Trogstad L2, Håberg SE2.

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3Journal of the Norwegian Medical Association, Oslo, Norway.

4Center for Infection and Immunity, Columbia University, NY, NY, USA.

**Abstract**

**BACKGROUND:** Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated to infections and it has been suggested that vaccination can trigger the disease. However, little is known about the specific association between clinically manifest influenza/influenza vaccine and CFS/ME. As part of a registry surveillance of adverse effects after mass vaccination in Norway during the 2009 influenza A (H1N1) pandemic, we had the opportunity to estimate and contrast the risk of CFS/ME after infection and vaccination.

**METHODS:** Using the unique personal identification number assigned to everybody who is registered as resident in Norway, we followed the complete Norwegian population as of October 1, 2009, through national registries of vaccination, communicable diseases, primary health, and specialist health care until December 31, 2012. Hazard ratios (HRs) of CFS/ME, as diagnosed in the specialist health care services (diagnostic code G93.3 in the International Classification of Diseases, Version 10), after influenza infection and/or vaccination were estimated using Cox proportional-hazards regression.

**RESULTS:** The incidence rate of CFS/ME was 2.08 per 100,000 person-months at risk. The adjusted HR of CFS/ME after pandemic vaccination was 0.97 (95% confidence interval [CI]: 0.91-1.04), while it was 2.04 (95% CI: 1.78-2.33) after being diagnosed with influenza infection during the peak pandemic period.

**CONCLUSIONS:** Pandemic influenza A (H1N1) infection was associated with a more than two-fold increased risk of CFS/ME. We found no indication of increased risk of CFS/ME after vaccination. Our findings are consistent with a model whereby symptomatic infection, rather than antigenic stimulation may trigger CFS/ME.

# Medical Hypotheses

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## Myalgic encephalomyelitis, chronic fatigue syndrome: An infectious disease

R.A. Underhill <sup>†,1</sup>

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abstract

The etiology of myalgic encephalomyelitis also known as chronic fatigue syndrome or ME/CFS has not been established. Controversies exist over whether it is an organic disease or a psychological disorder and even the existence of ME/CFS as a disease entity is sometimes denied. Suggested causal hypotheses have included psychosomatic disorders, infectious agents, immune dysfunctions, autoimmunity, metabolic disturbances, toxins and inherited genetic factors. Clinical, immunological and epidemiological evidence supports the hypothesis that: ME/CFS is an infectious disease; the causal pathogen persists in patients; the pathogen can be transmitted by casual contact; host factors determine susceptibility to the illness; and there is a population of healthy carriers, who may be able to shed the pathogen. ME/CFS is endemic globally as sporadic cases and occasional cluster outbreaks (epidemics). Cluster outbreaks imply an infectious agent. An abrupt flu-like onset resembling an infectious illness occurs in outbreak patients and many sporadic patients. Immune responses in sporadic patients resemble immune responses in other infectious diseases. Contagion is shown by finding secondary cases in outbreaks, and suggested by a higher prevalence of ME/CFS in sporadic patients' genetically unrelated close contacts (spouses/partners) than the community. Abortive cases, sub-clinical cases, and carrier state individuals were found in outbreaks. The chronic phase of ME/CFS does not appear to be particularly infective. Some healthy patient-contacts show immune responses similar to patients' immune responses, suggesting exposure to the same antigen (a pathogen). The chronicity of symptoms and of immune system changes and the occurrence of secondary cases suggest persistence of a causal pathogen. Risk factors which predispose to developing ME/CFS are: a close family member with ME/CFS; inherited genetic factors; female gender; age; rest/activity; previous exposure to stress or toxins; various infectious diseases preceding the onset of ME/CFS; and occupational exposure of health care professionals. The hypothesis implies that ME/CFS patients should not donate blood or tissue and usual precautions should be taken when handling patients' blood and tissue. No known pathogen has been shown to cause ME/CFS. Confirmation of the hypothesis requires identification of a causal pathogen. Research should focus on a search for unknown and known pathogens. Finding a causal pathogen could assist with diagnosis; help find a biomarker; enable the development of anti-microbial treatments; suggest preventive measures; explain pathophysiological findings; and reassure patients about the validity of their symptoms.

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## Is internet use unhealthy? A cross-sectional study of adolescent internet overuse

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### Summary

#### Abbreviations

aOR adjusted odds ratio

IAT internet addiction test

SES socioeconomic status

**OBJECTIVE:** To assess whether problematic internet use is associated with somatic complaints and whether this association remains when checking for internet activity among a random sample of adolescents living in the canton of Vaud, Switzerland.

**METHODS:** Cross-sectional survey of 3,067 8th graders (50.3% females) divided into average (n = 2,708) and problematic (n = 359) Internet users and compared for somatic complaints (backache, overweight, headaches, musculoskeletal pain, sleep problems and sight problems) controlling for sociodemographic and internet-related variables. Logistic regressions were performed for each complaint and for all of them simultaneously controlling variables significant at the bivariate level.

**RESULTS:** At the multivariate level, when taken separately, problematic internet users were more likely to have a chronic condition (adjusted odds ratio [aOR] with 95% CI: 1.58 [1.11:2.23]) and to report back pain (aOR: 1.46 [1.04:2.05]), overweight (aOR: 1.74 [1.03:2.93]), musculoskeletal pain (aOR: 1.36 [1.00:1.84]) and sleep problems (aOR: 2.16 [1.62:2.88]). When considered in the full model, only sleep problems remained significant (aOR: 2.03 [1.50:2.74]).

**CONCLUSIONS:** Our results confirm that problematic internet users report health problems more frequently, with lack of sleep being the most strongly associated and seeming to act as mediator regarding the other ones. Clinicians should remember to screen for excessive internet use their patients complaining of sleep-related problems, back or musculoskeletal pain or overweight. Clinicians should advise parents to limit the amount of time their adolescent children can spend online for leisure activities. Furthermore, limiting the number of devices used to connect to the internet could help warrant enough sleeping time.

**Key words:** adolescence; internet use; health status; adolescent behaviour

# Adolescent Sleep Patterns and Night-Time Technology Use: Results of the Australian Broadcasting Corporation's Big Sleep Survey

- Amanda L. Gamble,
- Angela L. D'Rozario,
- Delwyn J. Bartlett,
- Shaun Williams,
- Yu Sun Bin,
- Ronald R. Grunstein,
- Nathaniel S. Marshall



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## Abstract

### Introduction

Electronic devices in the bedroom are broadly linked with poor sleep in adolescents. This study investigated whether there is a dose-response relationship between use of electronic devices (computers, cellphones, televisions and radios) in bed prior to sleep and adolescent sleep patterns.

### Methods

Adolescents aged 11–17 yrs ( $n=1,184$ ; 67.6% female) completed an Australia-wide internet survey that examined sleep patterns, sleepiness, sleep disorders, the presence of electronic devices in the bedroom and frequency of use in bed at night.

### Results

Over 70% of adolescents reported 2 or more electronic devices in their bedroom at night. Use of devices in bed a few nights per week or more was 46.8% cellphone, 38.5% computer, 23.2% TV, and 15.8% radio. Device use had dose-dependent associations with later sleep onset on weekdays (highest-dose computer adjOR = 3.75: 99% CI = 2.17–6.46; cellphone 2.29: 1.22–4.30) and weekends (computer 3.68: 2.14–6.32; cellphone 3.24: 1.70–6.19; TV 2.32: 1.30–4.14), and later waking on weekdays (computer 2.08: 1.25–3.44; TV 2.31: 1.33–4.02) and weekends (computer 1.99: 1.21–3.26; cellphone 2.33: 1.33–4.08; TV 2.04: 1.18–3.55). Only ‘almost every night’ computer use (: 2.43: 1.45–4.08) was associated with short weekday sleep duration, and only ‘almost every night’ cellphone use (2.23: 1.26–3.94) was associated with wake lag (waking later on weekends).

### Conclusions

Use of computers, cell-phones and televisions at higher doses was associated with delayed sleep/wake schedules and wake lag, potentially impairing health and educational outcomes.

## Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) is different in children compared to in adults: a study of UK and Dutch clinical cohorts.

Collin SM<sup>1</sup>, Nuevo R<sup>1</sup>, van de Putte EM<sup>2</sup>, Nijhof SL<sup>2</sup>, Crawley E<sup>1</sup>.

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- <sup>2</sup>Department of Paediatrics, Wilhelmina Children's Hospital, University Medical Centre, Utrecht, The Netherlands.

### Abstract

#### **OBJECTIVE:**

To investigate differences between young children, adolescents and adults with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME).

#### **STUDY DESIGN:**

Comparison of clinical cohorts from 8 paediatric and 27 adult CFS/ME services in the UK and a paediatric randomised controlled trial from the Netherlands. Outcome measures include: fatigue (the UK-Chalder Fatigue Scale); Disability (the UK-SF-36 physical function subscale; the Netherlands-CHQ-CF87); school attendance, pain, anxiety and depression (the UK-Hospital Anxiety & Depression Scale, Spence Children's Anxiety Scale; the Netherlands-Spielberger State-Trait Anxiety Inventory for Children, Children's Depression Inventory); symptoms; time-to-assessment; and body mass index. We used multinomial regression to compare younger (aged <12 years) and older (aged 12-18 years) children with adults, and logistic regression to compare UK and Dutch adolescents.

#### **RESULTS:**

Younger children had a more equal gender balance compared to adolescents and adults. Adults had more disability and fatigue, and had been ill for longer. Younger children were less likely to have cognitive symptoms (OR 0.18 (95% CI 0.13 to 0.25)) and more likely to present with a sore throat (OR 1.42 (1.07 to 1.90)). Adolescents were more likely to have headaches (81.1%, OR 1.56 (1.36% to 1.80%)) and less likely to have tender lymph nodes, palpitations, dizziness, general malaise and pain, compared to adults. Adolescents were more likely to have comorbid depression (OR 1.51 (1.33 to 1.72)) and less likely to have anxiety (OR 0.46 (0.41 to 0.53)) compared to adults.

#### **CONCLUSIONS:**

Paediatricians need to recognise that children with CFS/ME present differently from adults. Whether these differences reflect an underlying aetiopathology requires further investigation.

#### **TRIAL REGISTRATION NUMBERS:**

FITNET trial registration numbers are ISRCTN59878666 and NCT00893438. This paper includes secondary (post-results) analysis of data from this trial, but are unrelated to trial outcomes.

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#### **KEYWORDS:**

EPIDEMIOLOGY; PAEDIATRICS

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# The effect of sleep deprivation on pain perception in healthy subjects: a meta-analysis

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## Highlights

- Sleep deprivation has a medium effect (SMD = 0.62) on pain perception.
- The calculated effect size is comparable with effect sizes achieved through pain treatment.
- Sleep deprivation affects self-reported pain as well as pain threshold.

## Abstract

### Background

There is strong evidence indicating an interaction between sleep and pain. However, the size of this effect, as well as the clinical relevance, is unclear. Therefore, this meta-analysis was conducted to quantify the effect of sleep deprivation on pain perception.

### Methods

A systematic literature search was conducted using the electronic databases PubMed, Cochrane, Psynindex, Psycinfo, and Scopus. By conducting a random-effect model, the pooled standardized mean differences (SMDs) of sleep deprivation on pain perception was calculated. Studies that investigated any kind of sleep deprivation in conjunction with a pain measurement were included. In cases of several pain measurements within a study, the average effect size of all measures was calculated.

### Results

Five eligible studies ( $N = 190$ ) for the between-group analysis and ten studies ( $N = 266$ ) for the within-group analysis were identified. Sleep deprivation showed a medium effect in the between-group analysis (SMD = 0.62; CI95: 0.12, 1.12;  $z = 2.43$ ;  $p = 0.015$ ) and a large effect in the within-group analysis (SMD = 1.49; CI95: 0.82, 2.17;  $z = 4.35$ ;  $p < 0.0001$ ). The test for heterogeneity was not significant in the between-group analysis ( $Q = 5.29$ ;  $df = 4$ ;  $p = 0.2584$ ), but it was significant in the within-group analysis ( $Q = 53.49$ ;  $df = 9$ ;  $p < 0.0001$ ).

### Conclusion

This meta-analysis confirms a medium effect (SMD = 0.62) of sleep deprivation on pain perception. As this meta-analysis is based on experimental studies in healthy subjects, the clinical relevance should be clarified.

### Keywords:

[Sleep deprivation](#), [Pain perception](#), [Meta-analysis](#), [Reciprocal relation](#)

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### **Less efficient and costly processes of frontal cortex in childhood chronic fatigue syndrome.**

Mizuno K, Tanaka M, Tanabe HC, Joudoi T, Kawatani J, Shigihara Y, Tomoda A, Miike T, Imai-Matsumura K, Sadato N, Watanabe Y.

#### **Abstract**

The ability to divide one's attention deteriorates in patients with childhood chronic fatigue syndrome (CCFS).

We conducted a study using a dual verbal task to assess allocation of attentional resources to two simultaneous activities (picking out vowels and reading for story comprehension) and functional magnetic resonance imaging. Patients exhibited a much larger area of activation, recruiting additional frontal areas.

The right middle frontal gyrus (MFG), which is included in the dorsolateral prefrontal cortex, of CCFS patients was specifically activated in both the single and dual tasks; this activation level was positively correlated with motivation scores for the tasks and accuracy of story comprehension. In addition, in patients, the dorsal anterior cingulate gyrus (dACC) and left MFG were activated only in the dual task, and activation levels of the dACC and left MFG were positively associated with the motivation and fatigue scores, respectively.

Patients with CCFS exhibited a wider area of activated frontal regions related to attentional resources in order to increase their poorer task performance with massive mental effort.

This is likely to be less efficient and costly in terms of energy requirements. It seems to be related to the pathophysiology of patients with CCFS and to cause a vicious cycle of further increases in fatigue.

## **Increased Vulnerability to Pattern-Related Visual Stress in Myalgic Encephalomyelitis**

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### **Abstract**

The objective of this study was to determine vulnerability to pattern-related visual stress in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). A total of 20 ME/CFS patients and 20 matched (age, gender) controls were recruited to the study.

Pattern-related visual stress was determined using the Pattern Glare Test. Participants viewed three patterns, the spatial frequencies (SF) of which were 0.3 (low-SF), 2.3 (mid-SF), and 9.4 (high-SF) cycles per degree (c/deg).

They reported the number of distortions they experienced when viewing each pattern. ME/CFS patients exhibited significantly higher pattern glare scores than controls for the mid-SF pattern. Mid-high SF differences were also significantly higher in patients than controls.

**These findings provide evidence of altered visual perception in ME/CFS.** Pattern-related visual stress may represent an identifiable clinical feature of ME/CFS that will prove useful in its diagnosis. However, further research is required to establish if these symptoms reflect ME/CFS-related changes in the functioning of sensory neural pathways.



Suzanne Vernon, PhD & Cynthia Bateman, M.D.

## **National Institute of Health Report for ME/CFS Research! What it Means for You**

By Suzanne D. Vernon, PhD

In case you missed it, ME/CFS, the Institute of Medicine report and the NIH have been all over the news the past few weeks. **The National Institutes of Health (NIH) announced that they are taking action to bolster research on myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).** NIH has taken their cue from the Institute of Medicine (IOM) that recommended new diagnostic criteria for ME/CFS in a report published in February 2015 [that] emphasized the need for safe and effective treatments since focusing on ME/CFS in 2012.

But perhaps the most persuasive influence on NIH and the other government agencies has come from the patients who have used technology to unite and make their voice heard. Social media, petitions, blogs (like occupycfs.com and healthrising.com) and websites (like MEAction.org) have made it impossible the government to ignore millions of people suffering with ME/CFS.

Perhaps all of the media coverage has left you wondering what this really means. Since Dr. Bateman was on the IOM committee that produced the landmark report and I worked for the government for almost 20 years, we thought we could help cut through the noise.

**First, here is what's happening at the NIH.** A study will start at the NIH Clinical Center –the world's largest research hospital – where only patients that participate in research on specific diseases are admitted. The details of the ME/CFS study have not yet been released but it looks like it will focus on ME/CFS patients that had a sudden, flu-like onset. **The main objective will be to understand what is going on at the biological and molecular level when someone develops ME/CFS following an infection.**

**This ME/CFS study is going to generate some long overdue BIG DATA!** I intend to be among the first to submit a BIG DATA analysis proposal to NIH.

**It was also announced that the Trans-NIH ME/CFS Research Working Group** will be chaired by the Director of the National Institute of Neurological Disorders and Stroke (NINDS), Walter J. Koroshetz, M.D. **This refreshed working group with new leadership will help reinvigorate, coordinate and support ME/CFS activities at NIH.** .

For far too long, the ME/CFS community has been diminished and dismissed. . A handful of researchers and doctors, like my colleague Dr. Bateman, have worked tirelessly to make change happen; champions that at times have worked at great personal sacrifice to forge a better way for our ME/CFS patient community. I believe it is all beginning to pay off. **The wheels of change move far too slowly on a federal level, but they are moving.** We are building a better future for all those impacted by ME/CFS. It is an exciting time to be on this journey with you!

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## **Serum Immune Proteins in Moderate and Severe Chronic Fatigue Syndrome/Myalgic Encephalomyelitis Patients**

Sharni Lee Hardcastle, Ekua Weba Brenu, Samantha Johnston, Thao Nguyen, Teilah Huth, Sandra Ramos, Donald Staines, and Sonya Marshall-Gradisnik

### **Abstract**

Immunological dysregulation is present in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), with recent studies also highlighting the importance of examining symptom severity.

This research addressed this relationship between CFS/ME severity subgroups, assessing serum immunoglobulins and serum cytokines in severe and moderate CFS/ME patients. Participants included healthy controls (n= 22), moderately (n = 22) and severely (n=19) affected CFS/ME patients.

The 1994 Fukuda Criteria defined CFS/ME and severity scales confirmed mobile and housebound CFS/ME patients as moderate and severe respectively. IL-1 $\beta$  was significantly reduced in severe compared with moderate CFS/ME patients. IL-6 was significantly decreased in moderate CFS/ME patients compared with healthy controls and severe CFS/ME patients. RANTES was significantly increased in moderate CFS/ME patients compared to severe CFS/ME patients.

Serum IL-7 and IL-8 were significantly higher in the severe CFS/ME group compared with healthy controls and moderate CFS/ME patients. **IFN- $\gamma$  was significantly increased in severe CFS/ME patients compared with moderately affected patients.**

This was the first study to show cytokine variation in moderate and severe CFS/ME patients, with significant differences shown between CFS/ME symptom severity groups.

This research suggests that distinguishing severity subgroups in CFS/ME research settings may allow for a more stringent analysis of the heterogeneous and otherwise inconsistent illness.

## **Persistence of impaired health status of Q fever patients 4 years after the first Dutch outbreak**

G. J. M. LIMONARD, J. B. PETERS, R. BESSELINK, C. A. R. GROOT, P. N. R. DEKHUIJZEN, J. H. VERCOULEN and M. H. NABUURS-FRANSSSEN

### **SUMMARY**

A significant proportion of Q fever patients from the first Dutch Q fever outbreak in 2007 showed impairment in health status up to 1 year after infection. Interested in whether this decrease in health status persisted, we set out to determine the health status in the same cohort of patients, 4 years after primary infection and to compare health status scores at the individual patient level between 1 and 4 years follow-up.

Health status was assessed with the Nijmegen Clinical Screening Instrument (NCSI). Patients were serologically tested to exclude patients with possible, probable or proven chronic Q fever.

Results on the NCSI sub-domains at group level [2008 (n = 54) and 2011 (n = 46)] showed a persistent significant percentage of patients exhibiting clinically relevant ('severe') scores for all NCSI sub-domains.

After 4 years, undue fatigue was present in 46% and exactly half of all patients experienced a severely impaired general quality of life. Patients with NCSI scores available in both 2008 and 2011 (n = 37) showed no difference in all sub-domain scores, except for a small decrease in dyspnoea emotions in 2011.

In this group, a significant proportion of patients either improved or worsened in one or more sub-domains of health status.

We conclude that at the group level, health status of Q fever patients remained impaired 4 years after primary infection. At the individual patient level, health status may change.

# Fatigue in adults with post-infectious fatigue syndrome: a qualitative content analysis

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The electronic version of this article is the complete one and can be found online at: <http://www.biomedcentral.com/1472-6955/14/64>

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## Abstract

### Background

Fatigue is a major problem among individuals with post-infectious fatigue syndrome (PIFS), also known as chronic fatigue syndrome or myalgic encephalomyelitis. It is a complex phenomenon that varies across illnesses. From a nursing perspective, knowledge and understanding of fatigue in this illness is limited. Nurses lack confidence in caring for these patients and devalue their professional role. The aim of this study was to explore in-depth the experiences of fatigue among individuals with PIFS. A detailed description of the phenomenon of fatigue is presented. Increased knowledge would likely contribute to more confident nurses and improved nursing care.

### Methods

A qualitative study with open interviews was employed. In-depth interviews with patients were fully transcribed and underwent a qualitative content analysis. A maximum variation sample of 26 affected adults between 26–59 years old was recruited from a population diagnosed at a fatigue outpatient clinic.

### Results

The fatigue was a post-exertional, multidimensional, fluctuating phenomenon with varying degrees of severity and several distinct characteristics and was accompanied by concomitant symptoms. Fatigue was perceived to be an all-pervasive complex experience that substantially reduced the ability to function personally or professionally. A range of trigger mechanisms evoked or worsened the fatigue, but the affected were not always aware of what triggered it. There was an excessive increase in fatigue in response to even minor activities. An increase in fatigue resulted in the exacerbation of other concomitant symptoms. The term fatigue does not capture the participants' experiences, which are accompanied by a considerable symptom burden that contributes to the illness experience and the severe disability.

### Conclusions

Although some aspects of the fatigue experience have been reported previously, more were added in our study, such as the dimension of awakening fatigue and the characteristic beyond time, when time passes unnoticed. We also identified trigger mechanisms such as emotional, neurological, social, financial, and pressure on oneself or from others. This in-depth exploration of fatigue in PIFS provides an overview of the dimensions, characteristics, and trigger mechanisms of fatigue, thus making better clinical observations, early recognition, improved communication with patients and more appropriate nursing interventions possible.