

CFS/ME Literature Review (Jan 2004 – Jun 2009)

A literature review has been included to help inform the workshop participants of the current state of research in the field.

A search on Scopus was run using the following search terms and limits:

Limits

Articles published or entered onto Scopus from 2004 – 2009.

Search Terms

A search was run using the following search terms:

CFS/ME OR chronic fatigue syndrome OR myalgic encephalomyelitis OR myalgic encephalopathy.

Autonomic dysfunction inc. cardiovascular abnormalities

Van Houdenhove B., Eede F.V.D., Luyten P.

Does hypothalamic-pituitary-adrenal axis hypofunction in chronic fatigue syndrome reflect a 'crash' in the stress system?

2009 Medical Hypotheses 72 (6); 701 - 705

<http://www.scopus.com/inward/record.url?eid=2-s2.0-62949099218&partnerID=40>

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The etiopathogenesis of chronic fatigue syndrome (CFS) remains poorly understood. Although neuroendocrine disturbances - and hypothalamic-pituitary-adrenal (HPA) axis hypofunction in particular - have been found in a large proportion of CFS patients, it is not clear whether these disturbances are cause or consequence of the illness. After a review of the available evidence we hypothesize that that HPA axis hypofunction in CFS, conceptualized within a system-biological perspective, primarily reflects a fundamental and persistent dysregulation of the neurobiological stress system. As a result, a disturbed balance between glucocorticoid and inflammatory signaling pathways may give rise to a pathological cytokine-induced sickness response that may be the final common pathway underlying central CFS symptoms, i.e. effort/stress intolerance and pain hypersensitivity. This comprehensive hypothesis on HPA axis hypofunction in CFS may stimulate diagnostic refinement of the illness, inform treatment approaches and suggest directions for future research, particularly focusing on the neuroendocrine-immune interface and possible links between CFS, early and recent life stress, and depression. © 2009 Elsevier Ltd. All rights reserved.

Smith A.K., Maloney E.M., Falkenberg V.R., Dimulescu I., Rajeevan M.S.

An angiotensin-1 converting enzyme polymorphism is associated with allostatic load mediated by C-reactive protein, interleukin-6 and cortisol

2009 Psychoneuroendocrinology 34 (4); 597 - 606

<http://www.scopus.com/inward/record.url?eid=2-s2.0-62549098578&partnerID=40>

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Allostatic load (AL) is a theoretical framework that describes the cumulative physiologic effects of adaptation to change or stress throughout the lifespan. AL is operationalized by a composite index of multiple biomarkers. Accordingly, genes, behavior and environment contribute to AL. To determine if individual differences in AL may be influenced by inherent genetic variation, we calculated an allostatic load index (ALI) for 182 Caucasian subjects derived from a population-based study of chronic fatigue syndrome. Nearly 65% of the subjects in this study sample reported fatiguing illness. ALI was calculated based on 11 measures representing metabolic, cardiovascular, inflammatory, hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) activities. Subjects were dichotomized into high (ALI \geq 3) or low (ALI < 3) AL groups, and the association between high AL and 129 polymorphisms in 32 genes related to the HPA axis, neurotransmission, inflammation, cardiovascular and metabolic functions were evaluated. Polymorphisms in angiotensin-1 converting enzyme (ACE), corticotropin-releasing hormone receptor 1 (CRHR1), and serotonin receptors (HTR3A and HTR4) were associated with AL ($p = 0.0007-0.0486$), but only one polymorphism, rs4968591, in ACE remained significant after correction for multiple comparisons. The T allele of ACE rs4968591 was more common in subjects with high AL (67.5%) than in subjects with low AL (49.3%) ($p = 0.0007$), and this effect appeared independent of age, sex, body mass index and fatigue status. Additionally, high interleukin-6 (IL-6; $p_{trend} = 0.04$), and C-reactive protein (CRP; $p_{trend} = 0.01$) levels, as well as low urinary cortisol levels in females ($p = 0.03$) were associated with the T allele, which may result in allele-specific binding of the transcription factor, E2F1. Our results suggest a role for ACE in the bidirectional communication between the central nervous and immune systems in response to stress. Further studies will be needed (a) to replicate the association between AL and ACE polymorphisms in

population studies designed to differentiate the effects of sex, age and racial/ethnic background, (b) to evaluate the effect of allele-specific binding of E2F1 at rs4968591, and (c) to examine the role of ACE in the co-regulation of CRP, IL-6 and cortisol.

Sakudo A., Kato Y.H., Tajima S., Kuratsune H., Ikuta K.

Visible and near-infrared spectral changes in the thumb of patients with chronic fatigue syndrome

2009 Clinica Chimica Acta 403 (01-Feb); 163 – 166

<http://www.scopus.com/inward/record.url?eid=2-s2.0-64849104310&partnerID=40>

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Background: Chronic fatigue syndrome (CFS) patients show a persistent fatigue condition with muscle pain and impairment of concentration, memory, and sleep. Presently, the physiological basis of CFS remains unclear. In this study, spectroscopic differences in the thumb were compared between 103 CFS patients and 122 healthy controls to examine possible changes of levels of oxygenated or deoxygenated hemoglobin. Methods: Visible and near-infrared (Vis-NIR) spectroscopy was used to examine possible changes in the region of 600-1100Å nm. Results: Vis-NIR spectra showed sharp peaks at 694, 970 and 1060Å nm and broad peaks in the regions of 740-760 and 830-850Å nm. As these peaks are possibly related to oxyhemoglobin, cytochrome c oxidase and water, levels of these factors were compared between the two groups. Statistical analysis of the absorbance of Vis-NIR spectra showed a significant decrease in water content, a significant increase in oxyhemoglobin content, and a significant increase in the oxidation of heme a + a₃ and copper in cytochrome c oxidase in CFS patients. Conclusions: These changes imply accelerated blood flow and energy metabolism in the thumbs of CFS patients. © 2009 Elsevier B.V. All rights reserved.

Newton J.L., Sheth A., Shin J., Pairman J., Wilton K., Burt J.A., Jones D.E.

Lower ambulatory blood pressure in chronic fatigue syndrome.

2009 Psychosomatic medicine 71 (3); 361 – 365

<http://www.scopus.com/inward/record.url?eid=2-s2.0-68549122686&partnerID=40>

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OBJECTIVE: To examine blood pressure circadian rhythm in subjects with chronic fatigue syndrome (CFS) and appropriate normal and fatigued controls to correlate parameters of blood pressure regulation with perception of fatigue in an observational cohort study. The cause of CFS remains unknown and there are no effective treatments. METHODS: To address whether inactivity was a confounder, we performed a 24-hour ambulatory blood pressure monitoring in the following three subject groups: 1) CFS patients (Fukuda Diagnostic criteria) (n = 38); 2) normal controls (n = 120); and 3) a fatigue comparison group (n = 47) with the autoimmune liver disease primary biliary cirrhosis (PBC). All patients completed a measure of fatigue severity (Fatigue Impact Scale). In view of the different demographics between the patient groups, patients were age- and sex-matched on a case-by-case basis to normal controls and blood pressure parameters were compared. RESULTS: Compared with the control population, the CFS group had significantly lower systolic blood pressure (p < .0001) and mean arterial blood pressure (p = .0002) and exaggerated diurnal variation (p = .009). There was a significant inverse relationship between increasing fatigue and diurnal variation of blood pressure in both the CFS and PBC groups (p < .05). CONCLUSION: Lower blood pressure and abnormal diurnal blood pressure regulation occur in patients with CFS. We would suggest the need for a randomized, placebo-controlled trial of agents to increase blood pressure such as midodrine in CFS patients with an autonomic phenotype.

Myhill S., Booth N.E., McLaren-Howard J.

Chronic fatigue syndrome and mitochondrial dysfunction

2009 International Journal of Clinical and Experimental Medicine 2 (1); 1 – 16

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65549089718&partnerID=40>

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This study aims to improve the health of patients suffering from chronic fatigue syndrome (CFS) by interventions based on the biochemistry of the illness, specifically the function of mitochondria in producing ATP (adenosine triphosphate), the energy currency for all body functions, and recycling ADP (adenosine diphosphate) to replenish the ATP supply as needed. Patients attending a private medical practice specializing in CFS were diagnosed using the Centers for Disease Control criteria. In consultation with each patient, an integer on the Bell Ability Scale was assigned, and a blood sample was taken for the "ATP profile" test, designed for CFS and other fatigue conditions. Each test produced 5 numerical factors which describe the availability of ATP in neutrophils, the fraction complexed with magnesium, the efficiency of oxidative phosphorylation, and the transfer efficiencies of ADP into the mitochondria and ATP into the cytosol where the energy is used. With the consent of each of 71 patients and 53 normal, healthy controls the 5 factors have been collated and compared with the Bell Ability Scale. The individual numerical factors show that patients have different combinations of biochemical lesions. When the factors are combined, a remarkable correlation is observed between the degree of mitochondrial dysfunction and the severity of illness ($P < 0.001$). Only 1 of the 71 patients overlaps the normal region. The "ATP profile" test is a powerful diagnostic tool and can differentiate patients who have fatigue and other symptoms as a result of energy wastage by stress and psychological factors from those who have insufficient energy due to cellular respiration dysfunction. The individual factors indicate which remedial actions, in the form of dietary supplements, drugs and detoxification, are most likely to be of benefit, and what further tests should be carried out.

Miwa K., Fujita M.

Cardiac function fluctuates during exacerbation and remission in young adults with chronic fatigue syndrome and "small heart"

2009 Journal of Cardiology 54 (1); 29 – 35

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650727261&partnerID=40>

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Background: "Small heart syndrome", previously referred to as so-called "neurocirculatory asthenia" associated with a small heart shadow on the chest roentgenogram, is characterized by weakness or fatigue even after mild exertion, palpitation, dyspnea, and fainting, many of which resemble symptoms in patients with chronic fatigue syndrome (CFS). Methods and results: The study population comprised 42 patients with CFS younger than 40 years of age. Cardiothoracic ratio was determined on the chest roentgenogram and echocardiographic examination was performed to evaluate both the cardiac chamber size and function. "Small heart" (cardiothoracic ratio $\geq 42\%$) on the chest X-ray photograph was noted in 26 (62%) of the study CFS patients. Echocardiographic examination demonstrated significantly smaller mean values of both the left ventricular (LV) end-diastolic and end-systolic dimensions, stroke volume indexes and cardiac indexes in CFS patients with "small heart" than in those without it and also in 20 control subjects. Thus, CFS patients with "small heart" had an actually small LV chamber and poor cardiac performance. During a long follow-up period of 10 CFS patients with "small heart", all echocardiographic parameters mentioned above improved and cardiothoracic ratios increased significantly during the remission phase as compared with exacerbation phase. Conclusions: "Small heart" on the chest X-ray photograph was prevalently noted in CFS patients. Echocardiographic examination revealed that CFS patients with "small heart" had an actually small LV chamber and poor cardiac performance. Cardiac functional changes evaluated by repeated examinations appeared to be directly associated with the severity of their symptoms. Small heart

syndrome with impaired cardiac function may contribute to the development of CFS through low cardiac output as a constitutional factor. © 2009 Japanese College of Cardiology.

Mathew S.J., Mao X., Keegan K.A., Levine S.M., Smith E.L.P., Heier L.A., Otcheretko V., Coplan J.D., Shungu D.C.

Ventricular cerebrospinal fluid lactate is increased in chronic fatigue syndrome compared with generalized anxiety disorder: An in vivo 3.0 T 1H MRS imaging study

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-64949160375&partnerID=40>

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Chronic fatigue syndrome (CFS) is a controversial diagnosis because of the lack of biomarkers for the illness and its symptom overlap with neuropsychiatric, infectious, and rheumatological disorders. We compared lateral ventricular volumes derived from tissue-segmented T1-weighted volumetric MRI data and cerebrospinal fluid (CSF) lactate concentrations measured by proton MRS imaging (1H MRSI) in 16 subjects with CFS (modified US Centers for Disease Control and Prevention criteria) with those in 14 patients with generalized anxiety disorder (GAD) and in 15 healthy volunteers, matched group-wise for age, sex, body mass index, handedness, and IQ. Mean lateral ventricular lactate concentrations measured by 1H MRSI in CFS were increased by 297% compared with those in GAD ($P < 0.001$) and by 348% compared with those in healthy volunteers ($P < 0.001$), even after controlling for ventricular volume, which did not differ significantly between the groups. Regression analysis revealed that diagnosis accounted for 43% of the variance in ventricular lactate. CFS is associated with significantly raised concentrations of ventricular lactate, potentially consistent with recent evidence of decreased cortical blood flow, secondary mitochondrial dysfunction, and/or oxidative stress abnormalities in the disorder. Copyright © 2008 John Wiley & Sons, Ltd.

Maloney E.M., Boneva R., Nater U.M., Reeves W.C.

Chronic fatigue syndrome and high allostatic load: results from a population-based case-control study in Georgia.

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650379422&partnerID=40>

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OBJECTIVE: To confirm the association of chronic fatigue syndrome (CFS) with high allostatic load (AL) level, examine the association of subsyndromal CFS with AL level, and investigate the effect of depression on these relationships and the association of AL with functional impairment, fatigue, symptom severity, fatigue duration, and type of CFS onset. AL represents the cumulative physiologic effect of demands to adapt to stress. **METHODS:** Population-based case-control study of 83 persons with CFS, 202 persons with insufficient symptoms or fatigue for CFS (ISF), and 109 well controls living in Georgia. Unconditional logistic regression was used to generate odds ratios (ORs) as measures of the association of AL with CFS. **RESULTS:** Relative to well controls, each 1-point increase in allostatic load index (ALI) was associated with a 26% increase in likelihood of having CFS ($OR(\text{adjusted}) = 1.26$, 95% Confidence Interval (CI) = 1.00, 1.59). This association remained in the presence and absence of depression ($OR(\text{adjusted}) = 1.35$, CI = 1.07, 1.72; $OR(\text{adjusted}) = 1.35$, CI = 1.10, 1.65). Compared with the ISF group, each 1-point increase in ALI was associated with a 10% increase in likelihood of having CFS ($OR(\text{adjusted}) = 1.10$, CI = 0.93, 1.31). Among persons with CFS, the duration of fatigue was inversely correlated with ALI ($r = -.26$, $p = .047$). **CONCLUSIONS:** Compared with well controls, persons with CFS were significantly more likely to have a high AL. AL increased in a gradient across well, ISF, and CFS groups.

Wyller V.B., Saul J.P., Walloe L., Thaulow E.

Sympathetic cardiovascular control during orthostatic stress and isometric exercise in adolescent chronic fatigue syndrome

2008 European Journal of Applied Physiology 102 (6); 623 – 632

<http://www.scopus.com/inward/record.url?eid=2-s2.0-39149112793&partnerID=40>

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The chronic fatigue syndrome (CFS) has been shown to be associated with orthostatic intolerance and cardiovascular dysregulation. We investigated the cardiovascular responses to combined orthostatic stress and isometric exercise in adolescents with CFS. We included a consecutive sample of 15 adolescents 12-18 years old with CFS diagnosed according to a thorough and standardized set of investigations, and a volunteer sample of 56 healthy control subjects of equal sex and age distribution. Heart rate, systolic, mean and diastolic blood pressure, stroke index, and total peripheral resistance index were non-invasively recorded during lower body negative pressure (LBNP) combined with two consecutive periods of handgrip. In addition, we measured baseline plasma catecholamines, and recorded symptoms. At rest, CFS patients had higher heart rate, diastolic blood pressure, plasma norepinephrine ($P < 0.01$), mean blood pressure and plasma epinephrine ($P < 0.05$) than controls. During LBNP, CFS patients had a greater increase in heart rate, diastolic blood pressure, mean blood pressure ($P < 0.05$) and total peripheral resistance index (n.s.) than controls. During handgrip, CFS patients had a smaller increase in heart rate, diastolic blood pressure ($P < 0.05$), mean blood pressure and total peripheral resistance index (n.s.) than controls. Our results indicate that adolescents with CFS have increased sympathetic activity at rest with exaggerated cardiovascular response to orthostatic stress, but attenuated cardiovascular response when performing isometric exercise during orthostatic stress. This suggests that CFS might be causally related to sympathetic dysfunction. © Springer-Verlag 2007.

Wyller V.B., Barbieri R., Thaulow E., Saul J.P.

Enhanced vagal withdrawal during mild orthostatic stress in adolescents with chronic fatigue

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-38449085647&partnerID=40>

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Background: Hemodynamic abnormalities have been documented in the chronic fatigue syndrome (CFS), indicating functional disturbances of the autonomic nervous system responsible for cardiovascular regulation. The aim of this study was to investigate autonomic heart rate control during mild orthostatic stress in adolescents with CFS. Methods: A total of 14 CFS patients and 56 healthy controls having equal distribution of age and gender underwent lower body negative pressure (LBNP) of 20 mmHg. The RR interval (RRI) was recorded continuously, and spectral power densities were computed in the low-frequency (LF) band (0.04-0.15 Hz) and the high-frequency (HF) band (0.15-0.50 Hz) from segments of 120-second length, using an autoregressive algorithm. In addition, the time-domain indices SDNN, pNN50, and r-MSSD were computed. Results: At rest, CFS had lower RRI than controls ($P < 0.05$), but indices of variability were similar in the two groups. During LBNP, compared to controls, CFS patients had lower normalized and absolute HF power and r-MSSD ($P < 0.05$), and higher RRI ($P < 0.001$), normalized LF power and LF/HF ($P < 0.05$). Conclusions: During mild orthostatic stress, adolescents with CFS appear to have enhanced vagal withdrawal, leading to a sympathetic predominance of heart rate control compared to controls. Possible underlying mechanisms include hypovolemia and abnormalities of reflex mechanisms. ©2008, Copyright the Authors.

Spence V.A., Kennedy G., Belch J.J.F., Hill A., Khan F.

Low-grade inflammation and arterial wave reflection in patients with chronic fatigue syndrome

2008 Clinical Science 114 (07-Aug); 561 – 566

<http://www.scopus.com/inward/record.url?eid=2-s2.0-41949091051&partnerID=40>

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Some of the symptoms reported by people with CFS (chronic fatigue syndrome) are associated with various cardiovascular phenomena. Markers of cardiovascular risk, including inflammation and oxidative stress, have been demonstrated in some patients with CFS, but little is known about the relationship between these and prognostic indicators of cardiovascular risk in this patient group. In the present study, we investigated the relationship between inflammation and oxidative stress and augmentation index, a measure of arterial stiffness, in 41 well-characterized patients with CFS and in 30 healthy subjects. Alx@75 (augmentation index normalized for a heart rate of 75 beats/min) was significantly greater in patients with CFS than in control subjects (22.5 ± 1.7 compared with 13.3 ± 2.3 % respectively; $P = 0.002$). Patients with CFS also had significantly increased levels of CRP (C-reactive protein) (2.58 ± 2.91 compared with 1.07 ± 2.16 μ g/ml respectively; $P < 0.01$) and 8-iso-prostaglandin F₂ isoprostanes (470.7 ± 250.9 compared with 331.1 ± 97.6 pg/ml respectively; $P < 0.005$). In patients with CFS, Alx@75 correlated significantly with logCRP ($r = 0.507$, $P = 0.001$), isoprostanes ($r = 0.366$, $P = 0.026$), oxidized LDL (low-density lipoprotein) ($r = 0.333$, $P = 0.039$) and systolic blood pressure ($r = 0.371$, $P = 0.017$). In a stepwise multiple regression model, including systolic and diastolic blood pressure, body mass index, CRP, tumour necrosis factor- α , interleukin-1, oxidized LDL, high-density lipoprotein-cholesterol levels, isoprostanes, age and gender, Alx@75 was independently associated with logCRP ($\hat{I}^2 = 0.385$, $P = 0.006$), age ($\hat{I}^2 = 0.363$, $P = 0.022$) and female gender ($\hat{I}^2 = 0.302$, $P = 0.03$) in patients with CFS. The combination of increased arterial wave reflection, inflammation and oxidative stress may result in an increased risk of future cardiovascular events. Assessment of arterial wave reflection might be useful for determining cardiovascular risk in this patient group. © 2008 Biochemical Society.

Paul L., Rafferty D., Wood L., Maclaren W.

Gait characteristics of subjects with chronic fatigue syndrome and controls at self-selected and matched velocities

2008 Journal of NeuroEngineering and Rehabilitation 5

<http://www.scopus.com/inward/record.url?eid=2-s2.0-45249097121&partnerID=40>

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Background. Gait abnormalities have been reported in individuals with Chronic Fatigue Syndrome (CFS) however no studies exist to date investigating the kinematics of individuals with CFS in over-ground gait. The aim of this study was to compare the over-ground gait pattern (sagittal kinematics and temporal and spatial) of individuals with CFS and control subjects at their self-selected and at matched velocities. **Methods.** Twelve individuals with CFS and 12 matched controls participated in the study. Each subject walked along a 7.2 m walkway three times at each of three velocities: self-selected, relatively slow (0.45 ms^{-1}) and a relatively fast (1.34 ms^{-1}). A motion analysis system was used to investigate the sagittal plane joint kinematics and temporal spatial parameters of gait. **Results.** At self-selected velocity there were significant differences between the two groups for all the temporal and spatial parameters measured, including gait velocity ($P = 0.002$). For the kinematic variables the significant differences were related to both ankles during swing and the right ankle during stance. At the relatively slower velocity the kinematic differences were replicated. However, the step distances decreased in the CFS population for the temporal and spatial parameters. When the gait pattern of the individuals with CFS at the relatively fast walking velocity ($1.30 \pm 0.24 \text{ ms}^{-1}$) was compared to the control subjects at their self-selected velocity ($1.32 \pm 0.15 \text{ ms}^{-1}$) the gait pattern of the two groups was very similar, with the exception of both ankles during swing. **Conclusion.** The self-selected gait velocity and/or pattern of individuals with CFS may be used to monitor the disease process or evaluate

therapeutic intervention. These differences may be a reflection of the relatively low self-selected gait velocity of individuals with CFS rather than a manifestation of the condition itself. © 2008 Paul et al; licensee BioMed Central Ltd.

Nijs J., Adriaens J., Schuermans D., Buyl R., Vincken W.

Breathing retraining in patients with chronic fatigue syndrome: A pilot study

2008 Physiotherapy Theory and Practice 24 (2);83 - 94

<http://www.scopus.com/inward/record.url?eid=2-s2.0-42449149178&partnerID=40>

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The study aimed to 1) examine the point prevalence of asynchronous breathing in chronic fatigue syndrome (CFS) patients; 2) examine whether CFS patients with an asynchronous breathing pattern present with diminished lung function in comparison with CFS patients with a synchronous breathing pattern; and 3) examine whether one session of breathing retraining in CFS patients with an asynchronous breathing pattern is able to improve lung function. Twenty patients fulfilling the diagnostic criteria for CFS were recruited for participation in a pilot controlled clinical trial with repeated measures. Patients presenting with an asynchronous breathing pattern were given 20-30 minutes of breathing retraining. Patients presenting with a synchronous breathing pattern entered the control group and received no intervention. Of the 20 enrolled patients with CFS, 15 presented with a synchronous breathing pattern and the remaining 5 patients (25%) with an asynchronous breathing pattern. Baseline comparison revealed no group differences in demographic features, symptom severity, respiratory muscle strength, or pulmonary function testing data (spirometry). In comparison to no treatment, the session of breathing retraining resulted in an acute (immediately postintervention) decrease in respiratory rate ($p < 0.001$) and an increase in tidal volume ($p < 0.001$). No other respiratory variables responded to the session of breathing retraining. In conclusion, the present study provides preliminary evidence supportive of an asynchronous breathing pattern in a subgroup of CFS patients, and breathing retraining might be useful for improving tidal volume and respiratory rate in CFS patients presenting with an asynchronous breathing motion. Copyright © Informa Healthcare.

Naschitz J.E., Slobodin G., Sharif D., Fields M., Isseroff H., Sabo E., Rosner I.

Electrocardiographic QT interval and cardiovascular reactivity in fibromyalgia differ from chronic fatigue syndrome

2008 European Journal of Internal Medicine 19 (3); 187 - 191

<http://www.scopus.com/inward/record.url?eid=2-s2.0-41349114598&partnerID=40>

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Background: Fibromyalgia (FM) and chronic fatigue syndrome (CFS) frequently overlap clinically and have been considered variants of one common disorder. We have recently shown that CFS is associated with a short corrected electrocardiographic QT interval (QTc). In the present study, we evaluated whether FM and CFS can be distinguished by QTc. Methods: The study groups were comprised of women with FM (n = 30) and with CFS (n = 28). The patients were evaluated with a 10 min supine-30 min head-up tilt test. The electrocardiographic QT interval was corrected for heart rate (HR) according to Fridericia's equation (QTc). In addition, cardiovascular reactivity was assessed based on blood pressure and HR changes and was expressed as the 'hemodynamic instability score' (HIS). Results: The average supine QTc in FM was 417 ms (SD 25) versus 372 ms (SD 22) in CFS ($p < 0.0001$); the supine QTc cut-off < 385.7 ms was 79% sensitive and 87% specific for CFS vs. FM. The average QTc at the 10th minute of tilt was 409 ms (SD 18) in FM versus 367 ms (SD 21) in CFS ($p < 0.0001$); the tilt QTc cut-off < 383.3 ms was 71% sensitive and 91% specific for CFS vs. FM. The average HIS in FM patients was - 3.52 (SD 1.96) versus + 3.21 (SD 2.43) in CFS ($p < 0.0001$).

Conclusion: A relatively short QTc and positive HIS characterize CFS patients and distinguish them from FM patients. These data may support the contention that FM and CFS are separate disorders. © 2007 European Federation of Internal Medicine.

Miwa K., Fujita M.

Small heart syndrome in patients with chronic fatigue syndrome

2008 Clinical Cardiology 31 (7); 328 – 333

<http://www.scopus.com/inward/record.url?eid=2-s2.0-47849092106&partnerID=40>

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Background: Small heart syndrome has previously been reported as neurocirculatory asthenia, associated with a small heart shadow on a chest roentgenogram. This is characterized as weakness or fatigue even after ordinary exertion, palpitation, dyspnea, and fainting, resembling patients with chronic fatigue syndrome (CFS). Hypothesis: Small heart syndrome may be prevalent in patients with CFS. Methods: The study population consisted of 56 patients (<50 y of age) with CFS, and 38 control subjects. Chest roentgenographic, echocardiographic, and physical examinations were performed. Results: Small heart syndrome (cardiothoracic ratio $\geq 42\%$) was significantly more prevalent in the CFS group (61%) than in the control group (24%) ($p < 0.01$). In CFS patients with a small heart ($n = 34$), narrow chest (88%), orthostatic dizziness (44%), foot coldness (41%), pretibial pitting edema (32%), r-kidney palpability (47%), and mitral valve prolapse (29%), were all significantly more prevalent than in the control group, and also in the CFS patients without small heart syndrome. Echocardiographic examination demonstrated significantly smaller values of both the left ventricular (LV) end-diastolic dimensions and end-systolic, and stroke volume and cardiac indexes in CFS with a small heart, as compared with control subjects with a normal heart size (42% < cardiothoracic ratio < 50%). Conclusions: A considerable number of CFS patients have a small heart, Small heart syndrome may contribute to the development of CFS as a constitutional factor predisposing to fatigue, and may be included in the genesis of CFS. © 2008 Wiley Periodicals, Inc.

Galland B.C., Jackson P.M., Sayers R.M., Taylor B.J.

A matched case control study of orthostatic intolerance in children/adolescents with chronic fatigue syndrome

2008 Pediatric Research 63 (2); 196 - 202

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This study aimed to define cardiovascular and heart rate variability (HRV) changes following head-up tilt (HUT) in children/adolescents with chronic fatigue syndrome (CFS) in comparison to age- and gender-matched controls. Twenty-six children/adolescents with CFS (11-19 y) and controls underwent 70-degree HUT for a maximum of 30 min, but returned to horizontal earlier at the participant's request with symptoms of orthostatic intolerance (OI) that included lightheadedness. Using electrocardiography and beat-beat finger blood pressure, a positive tilt was defined as OI with 1) neurally mediated hypotension (NMH); bradycardia (HR < 75% of baseline), and hypotension [systolic pressure (SysP) drops > 25 mm Hg] or 2) postural orthostatic tachycardia syndrome (POTS); HR increase > 30 bpm, or HR > 120 bpm (with/without hypotension). Thirteen CFS and five controls exhibited OI generating a sensitivity and specificity for HUT of 50.0% and 80.8%, respectively. POTS without hypotension occurred in seven CFS subjects but no controls. POTS with hypotension and NMH occurred in both. Predominant sympathetic components to HRV on HUT were measured in CFS tilt-positive subjects. In conclusion, CFS subjects were more susceptible to OI than controls, the cardiovascular response predominantly manifest as POTS without hypotension, a response unique to CFS suggesting further investigation is warranted with respect to the pathophysiologic mechanisms involved. © International Pediatrics Research Foundation, Inc. 2008. All Rights Reserved.

Bains W.

Treating Chronic Fatigue states as a disease of the regulation of energy metabolism

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Chronic Fatigue Syndrome is a physiological state in which the patient feels high levels of fatigue without an obvious organic cause, which affects around 1 in 400 people in the developed world. A wide range of causes have been suggested, including immune or hormonal dysfunction, viral or bacterial infection, and psychological somatization. It is likely that several causes are needed to trigger the disease, and that the triggers are different from the mechanisms that maintain fatigue over months or years. Many treatments have been tested for CFS, with very limited success - a programme of combined CBT and graded exercise shows the most effect. I suggest that patients with CFS have a reduced ability to increase mitochondrial energy production when exertion requires it, with fewer mitochondria that are each more efficient, and hence nearer to their maximum energy output, than normal. A range of indirect evidence suggests that the renin-angiotensin system stimulates mitochondrial responsiveness and reduces mitochondrial efficiency: chronic under-stimulation of this system could contribute to CFS aetiology. If correct, this means that CFS can be successfully treated with RAS agonists (eg angiotensin mimetics), or adrenergic agonists. It also suggests that there will be a positive link between the use of adrenergic- and RAS-blocking drugs and CFS incidence, and a negative link between adrenergic agonist use and CFS. © 2008 Elsevier Ltd. All rights reserved.

Wyller V.B., Thaulow E., Amlie J.P.

Treatment of Chronic Fatigue and Orthostatic Intolerance with Propranolol

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We describe the effect of propranolol in an adolescent with chronic fatigue syndrome and orthostatic intolerance. Our observations suggest that the head-up tilt-test and beta-blocker treatment might be considered in patients with chronic fatigue syndrome and that enhanced sympathetic nervous activity might be part of the underlying pathophysiology. © 2007 Mosby, Inc. All rights reserved.

Wyller V.B., Saul J.P., Amlie J.P., Thaulow E.

Sympathetic predominance of cardiovascular regulation during mild orthostatic stress in adolescents with chronic fatigue

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Haemodynamic abnormalities have been documented in the chronic fatigue syndrome (CFS), indicating functional disturbances of the autonomic nervous system responsible for cardiovascular control. This study was designed to explore the pathophysiology in adolescent CFS-patients by analysing RR-interval (RRI) variability and diastolic blood pressure (DBP) variability during mild orthostatic stress, using an algorithm which accounts for non-stationary biosignals. A total of 27 adolescents with CFS and 33 healthy control subjects having equal age- and sex distribution underwent 15min of 20° head-up tilt (HUT). The spectral power densities of RRI and DBP were computed in the low-frequency (LF) band (0.04-0.15Hz) and the high-frequency (HF) band (0.15-0.4Hz) using an adaptive autoregressive algorithm to obtain a time-varying spectrum. RMSSD, a time domain index of RRI variability, was also computed. At rest, all indices of variability were similar in the two groups. During tilt, CFS patients had a larger increase in the LF/HF ratio ($P = 0.001$) and normalized LF power of RRI ($P = 0.01$), and

a larger decrease in normalized HF power ($P \leq 0.01$) of RRI than controls. CFS patients also had trends towards a larger decrease in absolute HF power of RRI and a larger increase in normalized LF power of DBP. These findings suggest that adolescents with CFS have sympathetic predominance of cardiovascular regulation during very mild orthostatic stress. Possible underlying mechanisms are moderate hypovolemia, abnormalities of reflex control or physical de-conditioning. © 2007 The Authors Journal compilation © 2007 Blackwell Publishing Ltd.

Wyller V.B., Godang K., Morkrid L., Saul J.P., Thaulow E., Walloe L.

Abnormal thermoregulatory responses in adolescents with chronic fatigue syndrome: Relation to clinical symptoms

2007 Pediatrics 120 (1)

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OBJECTIVES. Chronic fatigue syndrome is a common and disabling disease of unknown etiology. Accumulating evidence indicates dysfunction of the autonomic nervous system. To further explore the pathophysiology of chronic fatigue syndrome, we investigated thermoregulatory responses dependent on catecholaminergic effector systems in adolescent patients with chronic fatigue syndrome. **PATIENTS AND METHODS.** A consecutive sample of 15 patients with chronic fatigue syndrome aged 12 to 18 years and a volunteer sample of 57 healthy control subjects of equal gender and age distribution were included. Plasma catecholamines and metanephrines were measured before and after strong cooling of 1 hand. Acral skin blood flow, tympanic temperature, heart rate, and mean blood pressure were measured during moderate cooling of 1 hand. In addition, clinical symptoms indicative of thermoregulatory disturbances were recorded. **RESULTS.** Patients with chronic fatigue syndrome reported significantly more shivering, sweating, sudden change of skin color, and feeling unusually warm. At baseline, patients with chronic fatigue syndrome had higher levels of norepinephrine, heart rate, epinephrine, and tympanic temperature than control subjects. During cooling of 1 hand, acral skin blood flow was less reduced, vasoconstrictor events occurred at lower temperatures, and tympanic temperature decreased more in patients with chronic fatigue syndrome compared with control subjects. Catecholamines increased and metanephrines decreased similarly in the 2 groups. **CONCLUSIONS.** Adolescent patients with chronic fatigue syndrome have abnormal catecholaminergic-dependent thermoregulatory responses both at rest and during local skin cooling, supporting a hypothesis of sympathetic dysfunction and possibly explaining important clinical symptoms. Copyright © 2007 by the American Academy of Pediatrics.

Wyller V.B., Due R., Saul J.P., Amlie J.P., Thaulow E.

Usefulness of an Abnormal Cardiovascular Response During Low-Grade Head-Up Tilt-Test for Discriminating Adolescents With Chronic Fatigue from Healthy Controls

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Hemodynamic dysfunction is documented in chronic fatigue syndrome (CFS). This study was conducted to investigate cardiovascular responses to orthostatic stress in adolescents with CFS, using a novel procedure for tilt-table testing. A total of 27 adolescents with CFS and 33 healthy control subjects with equal age and gender distribution underwent 15 minutes of 20° head-up tilt testing. Heart rate, systolic blood pressure (BP), mean BP, diastolic BP, stroke index, total peripheral resistance index, end-

diastolic volume index, and acceleration index were continuously and noninvasively recorded. At rest, patients with CFS had higher total peripheral resistance index values ($p < 0.01$) and lower stroke index and end-diastolic volume index values ($p < 0.05$) than controls. During 20° head-up tilt testing, patients with CFS had greater increases in heart rate, diastolic BP ($p < 0.001$), mean BP ($p < 0.01$), and total peripheral resistance index ($p < 0.05$) than controls and greater decreases in stroke index ($p < 0.05$). Syncope or near syncope was not observed. In conclusion, this study found that adolescents with CFS have significant abnormalities of cardiovascular regulation in response to mild orthostatic stress, differentiating them from healthy controls. © 2007 Elsevier Inc. All rights reserved.

Schmidt E.A., Payoux P., Darreon J., Voisin T., Esquerre J.P., Celsis P.
Flow/metabolism coupling in neurodegenerative disorders: A preliminary report

2007 Journal of Cerebral Blood Flow and Metabolism 27 (SUPPL. 1)
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Background and aims: Coupling and uncoupling between cerebral blood flow and metabolism is known in physiology and pathology. However, imaging of coupling has not been studied as a tool. We aim at defining new imaging techniques which might become a surrogate disease marker; uncoupling might herald pathological conditions. Two groups were studied: patients suffering of normal pressure hydrocephalus (NPH), and those complaining of chronic fatigue syndrome (CFS). Methods: 6 patients suspected of NPH (mean age 72), and 8 patients suspected of CFS (mean age 40) were enrolled. Each patient underwent the same day H215O PET and 18F-FDG PET. Firstly 2 injections of 300 Mbq of H215O were performed to measure rCBF in baseline condition. After 10 minutes, subjects underwent FDG PET, 20 minutes after an injection of 300 Mbq of 18F-FDG. To perform a voxel-based analysis we realigned the scans using a H215O and 18F-FDG normalized templates implemented in SPM2. A voxelwise unpaired t test was performed generating a t statistic map for the contrast condition effect after the specification of a design matrix. This was then converted to a Z map to assess statistical significance at a P level of 0.05. Uncoupling in regional cerebral CMRglu and rCBF, were investigated according to the general linear model in each voxel. Proportional scaling was applied by adjusting the mean global activity of each scan to 50 ml/100ml/min and the threshold of gray/white matter to 0.8. A voxel level threshold family wise error (FWE) was used with multicomparison test. We created an hybrid template (H215O and 18F-FDG) for this study, using a matlab function with all the FDG and H215O images of the subjects. Finally we compare FDG and H215O as contrast. Results: Using SPM2 at a FWE threshold with an hybrid template, we have been able to normalize our results especially irrespective of the ventricular dilation. We identified many uncoupling area in our group of NPH patients. In NPH hypermetabolism relative to rCBF was detected in various regions mainly bilateral occipital cortex. In CFS no specific pattern was identified. In both pathological conditions, hyperperfusion relative to metabolism was detected mainly around the vessels. Conclusion: We have been able to perform coupling and uncoupling images. Our preliminary results suggest that i) regions of relative hypermetabolism patterns can be identified within the brain, and ii) relative hyperperfusion is detected around the vessels, which is expected.

Niblett S.H., King K.E., Dunstan R.H., Clifton-Bligh P., Hoskin L.A., Roberts T.K., Fulcher G.R., McGregor N.R., Dunsmore J.C., Butt H.L., Klineberg I., Rothkirch T.B.
Hematologic and urinary excretion anomalies in patients with chronic fatigue syndrome

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Patients with chronic fatigue syndrome (CFS) have a broad and variable spectrum of signs and symptoms with variable onsets. This report outlines the results of a single-blind, cross-sectional research project that extensively investigated a large cohort of 100 CFS patients and 82 nonfatigued control subjects with the aim of performing a case-control evaluation of alterations in standard blood parameters and urinary amino and organic acid excretion profiles. Blood biochemistry and full blood counts were unremarkable and fell within normal laboratory ranges. However, the case-control comparison of the blood cell data revealed that CFS patients had a significant decrease in red cell distribution width and increases in mean platelet volume, neutrophil counts, and the neutrophil-lymphocyte ratio. Evaluation of the urine excretion parameters also revealed a number of anomalies. The overnight urine output and rate of amino acid excretion were both reduced in the CFS group ($P < 0.01$). Significant decreases in the urinary excretion of asparagine ($P < 0.0001$), phenylalanine ($P < 0.003$), the branch chain amino acids ($P < 0.005$), and succinic acid ($P < 0.0001$), as well as increases in 3-methylhistidine ($P < 0.05$) and tyrosine ($P < 0.05$) were observed. It was concluded that the urinary excretion and blood parameters data supported the hypothesis that alterations in physiologic homeostasis exist in CFS patients. Copyright © 2007 by the Society for Experimental Biology and Medicine.

Newton J.L., Okonkwo O., Sutcliffe K., Seth A., Shin J., Jones D.E.J.
Symptoms of autonomic dysfunction in chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-34547815646&partnerID=40>

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Background: Chronic fatigue syndrome (CFS) is common and its cause is unknown. Aim: To study the prevalence of autonomic dysfunction in CFS, and to develop diagnostic criteria. Design: Cross-sectional study with independent derivation and validation phases. Methods: Symptoms of autonomic dysfunction were assessed using the Composite Autonomic Symptom Scale (COMPASS). Fatigue was assessed using the Fatigue Impact Scale (FIS). Subjects were studied in two groups: phase 1 (derivation phase), 40 CFS patients and 40 age- and sex-matched controls; phase 2 (validation phase), 30 CFS patients, 37 normal controls and 60 patients with primary biliary cirrhosis. Results: Symptoms of autonomic dysfunction were strongly and reproducibly associated with the presence of CFS or primary biliary cirrhosis (PBC), and correlated with severity of fatigue. Total COMPASS score >32.5 was identified in phase 1 as a diagnostic criterion for autonomic dysfunction in CFS patients, and was shown in phase 2 to have a positive predictive value of 0.96 (95%CI 0.86-0.99) and a negative predictive value of 0.84 (0.70-0.93) for the diagnosis of CFS. Discussion: Autonomic dysfunction is strongly associated with fatigue in some, but not all, CFS and PBC patients. We postulate the existence of a 'cross-cutting' aetiological process of dysautonomia-associated fatigue (DAF). COMPASS >32.5 is a valid diagnostic criterion for autonomic dysfunction in CFS and PBC, and can be used to identify patients for targeted intervention studies. © The Author 2007. Published by Oxford University Press on behalf of the Association of Physicians.

Natelson B.H., Intriligator R., Cherniack N.S., Chandler H.K., Stewart J.M.

Hypocapnia is a biological marker for orthostatic intolerance in some patients with chronic fatigue syndrome

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Patients with chronic fatigue syndrome and those with orthostatic intolerance share many symptoms, yet questions exist as to whether CFS patients have physiological evidence of orthostatic intolerance.

Objective. To determine if some CFS patients have increased rates of orthostatic hypotension, hypertension, tachycardia, or hypocapnia relative to age-matched controls. Design. Assess blood pressure, heart rate, respiratory rate, end tidal CO₂ and visual analog scales for orthostatic symptoms when supine and when standing for 8 minutes without moving legs. Setting. Referral practice and research center. Participants. 60 women and 15 men with CFS and 36 women and 4 men serving as age matched controls with analyses confined to 62 patients and 35 controls showing either normal orthostatic testing or a physiological abnormal test. Main outcome measures. Orthostatic tachycardia; orthostatic hypotension; orthostatic hypertension; orthostatic hypocapnia or combinations thereof. Results. CFS patients had higher rates of abnormal tests than controls (53% vs 20%, $p < .002$), but rates of orthostatic tachycardia, orthostatic hypotension, and orthostatic hypertension did not differ significantly between patients and controls (11.3% vs 5.7%, 6.5% vs 2.9%, 19.4% vs 11.4%, respectively). In contrast, rates of orthostatic hypocapnia were significantly higher in CFS than in controls (20.6% vs 2.9%, $p < .02$). This CFS group reported significantly more feelings of illness and shortness of breath than either controls or CFS patients with normal physiological tests. Conclusion. A substantial number of CFS patients have orthostatic intolerance in the form of orthostatic hypocapnia. This allows subgrouping of patients with CFS and thus reduces patient pool heterogeneity engendered by use of a clinical case definition. © 2007 Natelson et al; licensee BioMed Central Ltd.

Javierre C., Alegre J., Ventura J.L., Garcia-Quintana A., Segura R., Suarez A., Morales A., Comella A., De Meirleir K.

Physiological responses to arm and leg exercise in women patients with chronic fatigue syndrome

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Patients affected by chronic fatigue syndrome (CFS) characteristically show easy and unexplained fatigue after minimal exertion that does not resolve with rest and is associated with specific symptoms lasting for more than six months. Cardiopulmonary exercise testing is a valid procedure for determining functional capacity in patients with CFS. We compare cardioventilatory adaptation to exercise between a group of eighty-five consecutive women patients affected by CFS and a group of fifteen healthy women extremely sedentary individuals, with the use of maximum incremental exercise testing on a cycle ergometer and arm ergometer, assessing possible differences. The majority of values achieved at peak exhaustive exercise were significantly lower in CFS patients than controls, including the percentage of maximum oxygen uptake in arm physical test ($37.4 \pm 10.0\%$ in CFS vs. $58.9 \pm 15.8\%$ in controls) and leg physical test ($53.4 \pm 15.0\%$ in CFS patients vs. $76.2 \pm 18.0\%$ in controls). In conclusion, the CFS group shows a lower work capacity in arm or leg exercise that would not be justified exclusively by their personal characteristics or deconditioning. Copyright © by The Haworth Press, Inc. All rights reserved.

Hannestad U., Theodorsson E., Evengard B.

\hat{I}^2 -Alanine and \hat{I}^3 -aminobutyric acid in chronic fatigue syndrome

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Background: Due to the occurrence of sleep disturbances and fatigue in chronic fatigue syndrome (CFS), an investigation was performed to examine if there is an abnormal excretion of \hat{I}^3 -aminobutyric

acid (GABA) and/or its structural analogue \hat{I}^2 -alanine in the urine from CFS patients. Both GABA and \hat{I}^2 -alanine are inhibitory neurotransmitters in the mammalian central nervous system. Methods: The 24 h urine excretion of GABA and \hat{I}^2 -alanine was determined by isotope dilution gas chromatography mass spectrometry in 33 CFS patients and 43 healthy controls. The degree of symptoms in both patients and controls was measured by grading of three typical CFS symptoms using a Visual Analogue Scale. Results: Men had a significantly higher excretion of both \hat{I}^2 -alanine and GABA than women. Comparing CFS patients with healthy controls showed no significant difference in excretion of neither \hat{I}^2 -alanine nor GABA. No correlation was found between the excretion of \hat{I}^2 -alanine or GABA and any of the three characteristic CFS symptoms measured. However, two female and two male CFS patients excreted considerably higher amounts of \hat{I}^2 -alanine in their 24 h urine samples than control subjects. Conclusions: Increased excretion of \hat{I}^2 -alanine was found in a subgroup of CFS patients, indicating that there may be a link between CFS and \hat{I}^2 -alanine in some CFS patients. © 2006 Elsevier B.V. All rights reserved.

Boneva R.S., Decker M.J., Maloney E.M., Lin J.-M., Jones J.F., Helgason H.G., Heim C.M., Rye D.B., Reeves W.C.

Higher heart rate and reduced heart rate variability persist during sleep in chronic fatigue syndrome: A population-based study

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-36148994716&partnerID=40>

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Autonomic nervous system (ANS) dysfunction has been suggested in patients with chronic fatigue syndrome (CFS). In this study, we sought to determine whether increased heart rate (HR) and reduced heart rate variability (HRV) parameters observed in CFS patients during wakefulness persist during sleep. To this end, we compared heart rate (HR) and HRV as indicators of ANS function in CFS subjects and non-fatigued (NF) controls in a population-based, case-control study. Thirty subjects with CFS and 38 NF controls, matched for age-, sex- and body mass index, were eligible for analysis. Main outcome measures included mean RR interval (RRI), HR, and HRV parameters derived from overnight ECG. Plasma aldosterone and norepinephrine levels, medicines with cardiovascular effect, and reported physical activity were examined as covariates. General Linear Models were used to assess significance of associations and adjust for potential confounders. Compared to controls, CFS cases had significantly higher mean HR (71.4 vs 64.8 bpm), with a shorter mean RRI [840.4 (85.3) vs 925.4(97.8) ms] ($p < 0.0004$, each), and reduced low frequency (LF), very low frequency (VLF), and total power (TP) of HRV ($p < 0.02$, all). CFS cases had significantly lower plasma aldosterone ($p < 0.05$), and tended to have higher plasma norepinephrine levels. HR correlated weakly with plasma norepinephrine ($r = 0.23$, $p = 0.05$) and moderately with vitality and fatigue scores ($r = -0.49$ and 0.46 , respectively, $p < 0.0001$). Limitation in moderate physical activity was strongly associated with increased HR and decreased HRV. Nevertheless, among 42 subjects with similar physical activity limitations, CFS cases still had higher HR (71.8 bpm) than respective controls (64.9 bpm), $p = 0.023$, suggesting that reduced physical activity could not fully explain CFS-associated differences in HR and HRV. After adjusting for potential confounders case-control differences in HR and TP remained significant ($p < 0.05$). Conclusion: the presence of increased HR and reduced HRV in CFS during sleep coupled with higher norepinephrine levels and lower plasma aldosterone suggest a state of sympathetic ANS predominance and neuroendocrine alterations. Future research on the underlying pathophysiologic mechanisms of the association is needed.

Bogaerts K., Hubin M., Van Diest I., De Peuter S., Van Houdenhove B., Van Wambeke P., Crombez G., Van den Bergh O.

Hyperventilation in patients with chronic fatigue syndrome: The role of coping strategies

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Hyperventilation has been suggested as a concomitant and possible maintaining factor that may contribute to the symptom pattern of chronic fatigue syndrome (CFS). Because patients accepting the illness and trying to live with it seem to have a better prognosis than patients chronically fighting it, we investigated breathing behavior during different coping response sets towards the illness in patients with CFS (N=30, CDC criteria). Patients imagined a relaxation script (baseline), a script describing a coping response of hostile resistance, and a script depicting acceptance of the illness and its (future) consequences. During each imagery trial, end-tidal PCO₂ (Handheld Capnograph, Oridion) was measured. After each trial, patients filled out a symptom checklist. Results showed low resting values of PetCO₂ overall, while only imagery of hostile resistance triggered a decrease and deficient recovery of PetCO₂. Also, more hyperventilation complaints and complaints of other origin were reported during hostile resistance imagery compared with acceptance and relaxation. In conclusion, hostile resistance seems to trigger both physiological and symptom perception processes contributing to the clinical picture of CFS. © 2007 Elsevier Ltd. All rights reserved.

Balasundaram B., Blake A.

Paroxysmal orthostatic tachycardia syndrome (POTS) with co-existing chronic fatigue syndrome: A review of three cases and discussion

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Orthostatic intolerance appears in many guises including overt dysautonomia, vasovagal syncope and orthostatic tachycardia. We present details of three patients referred to our syncope clinic, who satisfied the chronic fatigue criteria of the centre for disease control and prevention. Head-up tilt testing induced significant hypotension and increased heart rate in all three patients, consistent with the clinical and autonomic manifestations of postural orthostatic tachycardia syndrome. We report on the emerging evidence available which does suggest a direct relationship between these two syndromes.

Naschitz J.E., Mussafia-Priselac R., Kovalev Y., Zaigraykin N., Slobodin G., Elias N., Rosner I.

Patterns of hypocapnia on tilt in patients with fibromyalgia, chronic fatigue syndrome, nonspecific dizziness, and neurally mediated syncope

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33745264448&partnerID=40>

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OBJECTIVES: To assess whether head-up tilt-induced hyperventilation is seen more often in patients with chronic fatigue syndrome (CFS), fibromyalgia, dizziness, or neurally mediated syncope (NMS) as compared to healthy subjects or those with familial Mediterranean fever (FMF). **PATIENTS AND METHODS:** A total of 585 patients were assessed with a 10-minute supine, 30-minute head-up tilt test combined with capnography. Experimental groups included CFS (n = 90), non-CFS fatigue (n = 50),

fibromyalgia (n = 70), nonspecific dizziness (n = 75), and NMS (n = 160); control groups were FMF (n = 90) and healthy (n = 50). Hypocapnia, the objective measure of hyperventilation, was diagnosed when end-tidal pressure of CO₂ (PETCO₂) less than 30 mm Hg was recorded consecutively for 10 minutes or longer. When tilting was discontinued because of syncope, one PETCO₂ measurement of 25 or less was accepted as hyperventilation. RESULTS: Hypocapnia was diagnosed on tilt test in 9% to 27% of patients with fibromyalgia, CFS, dizziness, and NMS versus 0% to 2% of control subjects. Three patterns of hypocapnia were recognized: supine hypocapnia (n = 14), sustained hypocapnia on tilt (n = 76), and mixed hypotensive-hypocapnic events (n = 80). Hypocapnia associated with postural tachycardia syndrome (POTS) occurred in 8 of 41 patients. CONCLUSIONS: Hyperventilation appears to be the major abnormal response to postural challenge in sustained hypocapnia but possibly merely an epiphenomenon in hypotensive-hypocapnic events. Our study does not support an essential role for hypocapnia in NMS or in postural symptoms associated with POTS. Because unrecognized hypocapnia is common in CFS, fibromyalgia, and nonspecific dizziness, capnography should be a part of the evaluation of patients with such conditions. Copyright © by the Southern Society for Clinical Investigation.

Naschitz J., Fields M., Isseroff H., Sharif D., Sabo E., Rosner I.
Shortened QT interval: a distinctive feature of the dysautonomia of chronic fatigue syndrome

2006 Journal of Electrocardiology 39 (4); 389 – 394

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Purpose: Because autonomic nervous functioning is frequently abnormal in chronic fatigue syndrome (CFS), we examined whether the corrected QT interval (QTc) in CFS differs from QTc in other populations. Methods: The QTc was calculated at the end of 10 minutes of recumbence and the end of 10 minutes of head-up tilt. In a pilot study, groups of 15 subjects, CFS, and controls, matched for age and sex, were investigated. In a second phase of the study, the QTc was measured in larger groups of CFS (n = 30) and control patients (n = 96) not matched for demographic features. Results: In the pilot study, the average supine QTc in CFS was 0.371 ± 0.02 seconds and QTc on tilt, 0.385 ± 0.02 seconds, significantly shorter than in controls (P = .0002 and .0003, respectively). Results of phase II confirmed this data. Conclusions: Relative short QTc intervals are features of the CFS-related dysautonomia. The significance of this finding is discussed. © 2006 Elsevier Inc. All rights reserved.

Maloney E.M., Gurbaxani B.M., Jones J.F., de Souza Coelho L., Goertzel B.N.
Chronic fatigue syndrome and high allostatic load

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646025553&partnerID=40>

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Study population: We examined the relationship between chronic fatigue syndrome (CFS) and allostatic load in a population-based, case-control study of 43 CFS patients and 60 nonfatigued, healthy controls from Wichita, KS, USA. Methods: An allostatic load index was computed for all study participants using available laboratory and clinical data, according to a standard algorithm for allostatic load. Logistic regression analysis was used to compute odds ratios (ORs) as estimates of relative risk in models that included adjustment for matching factors and education; 95% confidence intervals (CIs) were computed to estimate the precision of the ORs. Results: CFS patients were 1.9-times more likely to have a high allostatic load index than controls (95% CI = 0.75, 4.75) after adjusting for education level, in addition to matching factors. The strength of this association increased in a linear trend across categories of low, medium and high levels of allostatic load (p = 0.06). Conclusion: CFS was associated with a high level of allostatic load. The three allostatic load components that best discriminated cases from controls were waist:hip ratio, aldosterone and urinary cortisol. © 2006 Future Medicine Ltd.

Kennedy G., Morris G., Spence V., McLaren M., Belch J.J.F.
Is chronic fatigue syndrome associated with platelet activation?

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646118483&partnerID=40>

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Chronic fatigue syndrome (CFS) is a debilitating condition that has no known aetiology or pathophysiology. Recent investigations by other workers have suggested that individuals with CFS may have a hypercoagulable state. This study investigated various aspects of platelet activation and function in 17 patients with CFS and in 16 age-matched and sex-matched healthy controls. Platelet aggregation, platelet volume and coagulation tests were performed. Platelet aggregation was investigated by means of the photometric changes using citrated platelet-rich plasma, whole blood aggregation was calculated as the percentage fall in single platelet counts and the coagulation tests were performed on an automatic microcentrifugal analyser. A trend was observed for the patients to have lower aggregation results and a reduced mean platelet volume. However, this only reached statistical significance for one result; the rate of the aggregation slope by 1.0 $\frac{1}{4}$ g/ml collagen [CFS patients, 18 (9-28) versus controls, 32.5 (19-36); Mann-Whitney U test, $P = 0.029$]. No significant differences were found for any of the measurements of coagulation. These results are in contrast to previously reported findings. However, due to the heterogeneous nature of the disease, and the resulting lifestyles of the patients, caution should be taken when comparing one group of patients with another. Nevertheless, we certainly found no evidence of increased platelet activation or of a hypercoagulable state in patients with CFS and, on the basis of these results, anti-platelet or anti-coagulant therapy is not warranted. © 2006 Lippincott Williams & Wilkins.

Goertzel B.N., Pennachin C., de Souza Coelho L., Maloney E.M., Jones J.F., Gurbaxani B.
Allostatic load is associated with symptoms in chronic fatigue syndrome patients

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646052869&partnerID=40>

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Objectives: To further explore the relationship between chronic fatigue syndrome (CFS) and allostatic load (AL), we conducted a computational analysis involving 43 patients with CFS and 60 nonfatigued, healthy controls (NF) enrolled in a population-based case-control study in Wichita (KS, USA). We used traditional biostatistical methods to measure the association of high AL to standardized measures of physical and mental functioning, disability, fatigue and general symptom severity. We also used nonlinear regression technology embedded in machine learning algorithms to learn equations predicting various CFS symptoms based on the individual components of the allostatic load index (ALI). Methods: An ALI was computed for all study participants using available laboratory and clinical data on metabolic, cardiovascular and hypothalamic-pituitary-adrenal (HPA) axis factors. Physical and mental functioning/impairment was measured using the Medical Outcomes Study 36-item Short Form Health Survey (SF-36); current fatigue was measured using the 20-item multidimensional fatigue inventory (MFI); frequency and intensity of symptoms was measured using the 19-item symptom inventory (SI). Genetic programming, a nonlinear regression technique, was used to learn an ensemble of different predictive equations rather than a single one. Statistical analysis was based on the calculation of the percentage of equations in the ensemble that utilized each input variable, producing a measure of the 'utility' of the variable for the predictive problem at hand. Traditional biostatistics methods include the median and Wilcoxon tests for comparing the median levels of subscale scores obtained on the SF-36, the MFI and the SI summary score. Results: Among CFS patients, but not controls, a high level of AL was significantly associated with lower median values (indicating worse health) of bodily pain, physical functioning and general symptom frequency/intensity. Using genetic programming, the ALI was determined to be a better predictor of these three health measures than any subcombination of ALI components among cases, but not controls. © 2006 Future Medicine Ltd.

Cook D.B., Nagelkirk P.R., Poluri A., Mores J., Natelson B.H.

The influence of aerobic fitness and fibromyalgia on cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome

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Objective. To investigate cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome (CFS), accounting for comorbid fibromyalgia (FM) and controlling for aerobic fitness. **Methods.** Twenty-nine patients with CFS only, 23 patients with CFS plus FM, and 32 controls completed an incremental bicycle test to exhaustion. Cardiorespiratory and perceptual responses were measured. Results were determined for the entire sample and for 18 subjects from each group matched for peak oxygen consumption. **Results.** In the overall sample, there were no significant differences in cardiorespiratory parameters between the CFS only group and the controls. However, the CFS plus FM group exhibited lower ventilation, lower end-tidal CO₂, and higher ventilatory equivalent of carbon dioxide compared with controls, and slower increases in heart rate compared with both patients with CFS only and controls. Peak oxygen consumption, ventilation, and workload were lower in the CFS plus FM group. Subjects in both the CFS only group and the CFS plus FM group rated exercise as more effortful than did controls. Patients with CFS plus FM rated exercise as significantly more painful than did patients with CFS only or controls. In the subgroups matched for aerobic fitness, there were no significant differences among the groups for any measured cardiorespiratory response, but perceptual differences in the CFS plus FM group remained. **Conclusion.** With matching for aerobic fitness, cardiorespiratory responses to exercise in patients with CFS only and CFS plus FM are not different from those in sedentary healthy subjects. While CFS patients with comorbid FM perceive exercise as more effortful and painful than do controls, those with CFS alone do not. These results suggest that aerobic fitness and a concurrent diagnosis of FM are likely explanations for currently conflicting data and challenge ideas implicating metabolic disease in the pathogenesis of CFS. © 2006, American College of Rheumatology.

Van De Putte E.M., Uiterwaal C.S.P.M., Bots M.L., Kuis W., Kimpfen J.L.L., Engelbert R.H.H.

Is chronic fatigue syndrome a connective tissue disorder? A cross-sectional study in adolescents

2005 Pediatrics 115 (4)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-23244462082&partnerID=40>

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Objectives. To investigate whether constitutional laxity of the connective tissues is more frequently present in adolescents with chronic fatigue syndrome (CFS) than in healthy controls. Increased joint hypermobility in patients with CFS has been previously described, as has lower blood pressure in fatigued individuals, which raises the question of whether constitutional laxity is a possible biological predisposing factor for CFS. **Design.** Cross-sectional study. **Participants.** Thirty-two adolescents with CFS (according to the criteria of the Centers for Disease Control and Prevention) referred to a tertiary hospital and 167 healthy controls. **Methods.** The 32 adolescents with CFS were examined extensively regarding collagen-related parameters: joint mobility, blood pressure, arterial stiffness and arterial wall thickness, skin extensibility, and degradation products of collagen metabolism. Possible confounding factors (age, gender, height, weight, physical activity, muscle strength, diet, alcohol consumption, and cigarette smoking) were also measured. The results were compared with findings in 167 healthy adolescents who underwent the same examinations. **Results.** Joint mobility, Beighton score, and

collagen biochemistry, all indicators of connective tissue abnormality, were equal for both groups. Systolic blood pressure, however, was remarkably lower in patients with CFS (117.3 vs. 129.7 mm Hg; adjusted difference: -13.5 mm Hg; 95% confidence interval [CI]: - 19.1, -7.0). Skin extensibility was higher in adolescents with CFS (mean z score: 0.5 vs. 0.1 SD; adjusted difference: 0.3 SD; 95% CI: 0.1, 0.5). Arterial stiffness, expressed as common carotid distension, was lower in adolescents with CFS, indicating stiffer arteries (670 vs 820 $\hat{I}\frac{1}{4}$ m; adjusted difference: -110 $\hat{I}\frac{1}{4}$ m; 95% CI: -220, -10). All analyses were adjusted for age, gender, body mass index, and physical activity. Additionally, arterial stiffness was adjusted for lumen diameter and pulse pressure. Conclusions. These findings do not consistently point in the same direction of an abnormality in connective tissue. Patients with CFS did have lower blood pressure and more extensible skin but lacked the most important parameter indicating constitutional laxity, ie, joint hypermobility. Moreover, the collagen metabolism measured by crosslinks and hydroxyproline in urine, mainly reflecting bone resorption, was not different. The unexpected finding of stiffer arteries in patients with CFS warrants additional investigation. Copyright © 2005 by the American Academy of Pediatrics.

Jones J.F., Nicholson A., Nisenbaum R., Papanicolaou D.A., Solomon L., Boneva R., Heim C., Reeves W.C.

Orthostatic instability in a population-based study of chronic fatigue syndrome

2005 American Journal of Medicine 118 (12)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-29244463853&partnerID=40>

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PURPOSE: Autonomic nervous system dysfunction has been suggested as involved in the pathophysiology of chronic fatigue syndrome. This population-based case control study addressed the potential association between orthostatic instability (one sign of dysautonomia) and chronic fatigue syndrome. **SUBJECTS AND METHODS:** Fifty-eight subjects who fulfilled criteria of the 1994 chronic fatigue syndrome research case definition and 55 healthy controls participated in a 2-day inpatient evaluation. Subjects had been identified during a 4-year population-based chronic fatigue syndrome surveillance study in Wichita, Kan. The present study evaluated subjects' current medical and psychiatric status, reviewed past medical/psychiatric history and medication use, used a stand-up test to screen for orthostatic instability, and conducted a head-up tilt table test to diagnose orthostatic instability. **RESULTS:** No one manifested orthostatic instability in the stand-up test. The head-up tilt test elicited orthostatic instability in 30% of eligible chronic fatigue syndrome subjects (all with postural orthostatic tachycardia) and 48% of controls (50% with neurally mediated hypotension); intolerance was present in only nonfatigued (n = 7) subjects. Neither fatigue nor illness severity were associated with outcome. **CONCLUSIONS:** Orthostatic instability was similar in persons with chronic fatigue syndrome and nonfatigued controls subjects recruited from the general Wichita population. Delayed responses to head-up tilt tests were common and may reflect hydration status. These findings suggest reappraisal of primary dysautonomia as a factor in the pathogenesis of chronic fatigue syndrome. © 2005 Elsevier Inc. All rights reserved.

Yoshiuchi K., Quigley K.S., Ohashi K., Yamamoto Y., Natelson B.H.

Use of time-frequency analysis to investigate temporal patterns of cardiac autonomic response during head-up tilt in chronic fatigue syndrome

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Although a number of studies have reported alterations in cardiac autonomic nervous system function in chronic fatigue syndrome (CFS), the results are not consistent across studies. Reasons for these discrepancies include (1) the use of a heterogeneous patient sample that included those with orthostatic postural tachycardia (POTS), a condition with an autonomic changes, and (2) the use of frequency domain techniques which require a stationary signal and averaging data across relatively long epochs. To deal with these shortcomings, we used the smoothed pseudo-Wigner-Ville transform (SPWVT) to analyze heart rate variability (HRV) and blood pressure variability (BPV) during head-up tilt (HUT) by separating CFS patients into those with and without POTS. SPWVT has the advantage of providing instantaneous information about autonomic function under nonstable physiological conditions. We studied 18 CFS patients without POTS, eight CFS patients with POTS and 25 sedentary healthy controls during supine rest and during the first 10 min after HUT. While we found significant effects of postural change in both groups for all autonomic variables, there were significant group \times time interactions between CFS without POTS and controls for only instant center frequency (ICF) within the low frequency region both from HRV ($p=0.02$) and from BPV ($p=0.01$). Although the physiological meaning of ICF still remains unknown, the data suggest that even CFS patients without POTS may have a subtle underlying disturbance in autonomic function. © 2004 Elsevier B.V. All rights reserved.

Winkler A.S., Blair D., Marsden J.T., Peters T.J., Wessely S., Cleare A.J.
Autonomic function and serum erythropoietin levels in chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-1542358048&partnerID=40>

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Objective Given previous findings, we wished to investigate whether there was evidence of autonomic dysfunction in patients with chronic fatigue syndrome, and whether this could be related to reduced erythropoietin levels and altered red blood cell indices. Methods We assessed autonomic function and analysed blood parameters (including erythropoietin) in 22 patients with chronic fatigue syndrome who were medication-free and without comorbid depression or anxiety. Results were compared to 23 iron-deficiency anaemia patients and 18 healthy individuals. Results Autonomic testing in patients with chronic fatigue syndrome yielded a significantly greater increase in heart rate together with a more pronounced systolic blood pressure fall on standing compared to healthy individuals. Heart rate beat-to-beat variation on deep breathing and responses to the Valsalva manoeuvre were normal. Two of 22 patients with chronic fatigue had mild normochromic normocytic anaemia with normal ferritin, vitamin B12 and folate levels. Serum erythropoietin levels were within reference range. Conclusion Some autonomic dysfunction is present in chronic fatigue syndrome (CFS) patients; the explanation remains uncertain, but could relate to cardiovascular deconditioning. There were no major haematological, biochemical or immunological abnormalities in these patients. © 2004 Elsevier Inc. All rights reserved.

Spence V.A., Khan F., Kennedy G., Abbot N.C., Belch J.J.F.
Acetylcholine mediated vasodilatation in the microcirculation of patients with chronic fatigue syndrome

2004 Prostaglandins Leukotrienes and Essential Fatty Acids 70 (4); 403 – 407
<http://www.scopus.com/inward/record.url?eid=2-s2.0-1842505974&partnerID=40>

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The aetiology of chronic fatigue syndrome (CFS) remains controversial and a number of hypotheses have been put forward to explain it. Research into the condition is hindered by the considerable

heterogeneity seen across patients but several reports have highlighted disturbances to cholinergic mechanisms in terms of central nervous system activity, neuromuscular function and autoantibodies to muscarinic cholinergic receptors. This paper examines an altogether separate function for acetylcholine and that is its role as an important and generalized vasodilator. Most diseases are accompanied by a blunted response to acetylcholine but the opposite is true for CFS. Such sensitivity is normally associated with physical training so the finding in CFS is anomalous and may well be relevant to vascular symptoms that characterise many patients. There are several mechanisms that might lead to ACh endothelial sensitivity in CFS patients and various experiments have been designed to unravel the enigma. These are reported here. © 2004 Elsevier Ltd. All rights reserved.

Puri B.K., Holmes J., Hamilton G.

Eicosapentaenoic acid-rich essential fatty acid supplementation in chronic fatigue syndrome associated with symptom remission and structural brain changes

2004 International Journal of Clinical Practice 58 (3); 297 – 299

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Lateral ventricular enlargement has been reported in chronic fatigue syndrome, while cerebral neurospectroscopy has recently indicated that essential fatty acid treatment may be of value in this condition. An essential fatty acid supplement rich in eicosapentaenoic acid (EPA) was therefore given daily to a female patient with a 6-year history of unremitting symptoms of chronic fatigue syndrome. Cerebral magnetic resonance scanning was carried out at baseline and 16 weeks later. The EPA-rich essential fatty acid supplementation led to a marked clinical improvement in her symptoms of chronic fatigue syndrome, starting within 6-8 weeks. Accurate quantification of the lateral ventricular volumes in the baseline and 16-week follow-up registered images of high-resolution magnetic resonance imaging structural scans showed that the treatment was accompanied by a marked reduction in the lateral ventricular volume during this period, from 28 940-23 660 mm³. © 2004 Blackwell Publishing Ltd.

Nijs J., De Meirleir K.

Prediction of peak oxygen uptake in patients fulfilling the 1994 CDC criteria for chronic fatigue syndrome

2004 Clinical Rehabilitation 18 (7); 785 – 792

<http://www.scopus.com/inward/record.url?eid=2-s2.0-9144255592&partnerID=40>

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Purpose: To establish an inexpensive, simple method of predicting peak oxygen uptake [Vo₂peak) in patients fulfilling the 1994 Centers for Disease Control and Prevention (CDC) criteria for chronic fatigue syndrome (CFS). Design: A retrospective observational study. Setting: An outpatient tertiary care chronic fatigue clinic. Subjects: Two hundred and forty consecutive patients fulfilling the 1994 CDC criteria for CFS. Interventions: Heart rate, metabolic and ventilatory parameters were measured continuously during a maximal exercise stress test on a bicycle ergometer. Using the equation peak oxygen uptake = 13.1 \bar{A} — peak workload+284 (used by Mullis et al., Br J Sports Med 1999; 33: 352-56), Vo₂peak was predicted from the peak workload of a maximal exercise capacity test. Pearson correlation coefficient and linear regression analysis were used to establish the most accurate way to predict Vo₂peak. Results: Percentage error encountered when comparing actual measured Vo₂peak with predicted value was 17.3% (\bar{A} ± 10.0). A strong correlation between Vo₂peak and peak workload was observed (r = 0.89, p < 0.001). A regression analysis established the relation as Vo₂peak = 10.47 \bar{A} — peak workload +284.1, where Vo₂peak is given in ml/min and peak workload in W (error in prediction = 11.0 \bar{A} ±9.5%). Conclusions: Monitoring of the peak workload during a maximal, graded bicycle ergometric test suffices to predict the Vo₂peak. When predicting Vo₂peak the used operational definition for the diagnosis of CFS could be taken into account. Compared with the equation used by

Mullis et al., peak workload is multiplied by 10.47 in order to predict peak oxygen uptake in CDC-defined CFS patients. © Arnold 2004.

Naschitz J.E., Rosner I., Rozenbaum M., Fields M., Isseroff H., Babich J.P., Zuckerman E., Elias N., Yeshurun D., Naschitz S., Sabo E.

Patterns of cardiovascular reactivity in disease diagnosis

2004 QJM - Monthly Journal of the Association of Physicians 97 (3); 141 – 151

<http://www.scopus.com/inward/record.url?eid=2-s2.0-12144290841&partnerID=40>

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Background: Aberrations of cardiovascular reactivity (CVR), an expression of autonomic function, occur in a number of clinical conditions, but lack specificity for a particular disorder. Recently, a CVR pattern particular to chronic fatigue syndrome was observed. Aim: To assess whether specific CVR patterns can be described for other clinical conditions. Methods: Six groups of patients, matched for age and gender, were evaluated with a shortened head-up tilt test: patients with chronic fatigue syndrome (CFS) (n=20), non-CFS fatigue (F) (n=15), neurally-mediated syncope (SY) (n=21), familial Mediterranean fever (FMF) (n=17), psoriatic arthritis (PSOR) (n=19) and healthy subjects (H) (n=20). A 10-min supine phase was followed by recording 600 cardiac cycles on tilt (5-10 min). Beat-to-beat heart rate (HR) and pulse transit time (PTT) were measured. Results were analysed using conventional statistics, recurrence plot analysis and fractal analysis. Results: Multivariate analysis evaluated independent predictors of the CVR in each patient group vs. all other groups. Based on these predictors, equations were determined for a linear discriminant score (DS) for each group. The best sensitivities and specificities of the DS, consistent with disease-related phenotypes of CVR, were noted in the following groups: CFS, 90.0% and 60%; SY, 93.3% and 62.5%; FMF, 90.1% and 75.4%, respectively. Discussion: Pathological disturbances may alter cardiovascular reactivity. Our data support the existence of disease-related CVR phenotypes, with implications for pathogenesis and differential diagnosis. © Association of Physicians 2004; all rights reserved.

Naschitz J., Dreyfuss D., Yeshurun D., Rosner I.

Midodrine treatment for chronic fatigue syndrome

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The long term results of midodrine treatment in a patient having debilitating chronic fatigue syndrome (CFS) are reported. Midodrine treatment, directed at the autonomic nervous system, resulted in correction of the dysautonomia followed by improvement of fatigue. This finding is consistent with the hypothesis that dysautonomia plays a major part in the pathophysiology of CFS and that therapies directed at the autonomic nervous system may be effective in the treatment of CFS.

Lucas K.E., Rowe P.C., Coresh J., Klag M.J., Meoni L.A., Ford D.E.

Prospective association between hypotension and idiopathic chronic fatigue

2004 Journal of Hypertension 22 (4); 691 – 695

<http://www.scopus.com/inward/record.url?eid=2-s2.0-2142751068&partnerID=40>

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Objective: To determine whether there is an association between hypotension and incident cases of idiopathic chronic fatigue. Design: A prospective study. Setting: Johns Hopkins Precursors Study.

Participants: Medical students (n = 876) in graduating classes from 1948 to 1964. Main outcome measure: 'Easy fatigability' reported by participants at 5- or 10-year follow-up after graduation. Results: The unadjusted risk in women was 5.0 (95% exact confidence interval = 1.4 to 17.4) and in men was 1.7 (95% exact confidence interval = 0.8, to 3.5). Conclusion: These preliminary findings suggest that hypotension may be a risk factor for the development of idiopathic chronic fatigue in women. A© 2004 Lippincott Williams & Wilkins.

Khan F., Kennedy G., Spence V.A., Newton D.J., Belch J.J.F.
Peripheral cholinergic function in humans with chronic fatigue syndrome, Gulf War syndrome and with illness following organophosphate exposure

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-1242284394&partnerID=40>

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In the present study, we have investigated whether the peripheral cholinergic abnormalities that we have reported previously [Spence, Khan and Belch (2000) Am. J. Med. 108, 736-739] in patients with chronic fatigue syndrome (CFS) are also present in those with Gulf War syndrome (GWS) and agricultural workers exposed to organophosphate pesticides, where cholinesterase inhibition is specifically implicated. We also looked at whether these abnormalities might be due to a reduction in the activity of cholinesterase expressed on the vascular endothelium. We used laser Doppler imaging to measure the forearm skin blood flow responses to iontophoresis of acetylcholine and of methacholine (which is resistant to breakdown by cholinesterase) in patients with CFS, GWS and those with a history of ill health after definite organophosphate exposure, as well as in matched healthy controls. The response to acetylcholine was significantly higher in patients with CFS than in controls (P = 0.029, repeated-measures ANOVA), but was normal in those with GWS and those exposed to organophosphates. The methacholine response was higher than the acetylcholine response in all patient groups except for those with CFS, where there was no difference between the responses. Although there are many clinical similarities between these three illnesses, our results indicate peripheral cholinergic abnormalities in the vascular endothelium of only patients with CFS, suggesting that this syndrome has a different aetiology, which might involve inhibition of vascular cholinesterase.

Donnelly D.L., Rockland R.H., Reisman S.S., Quigley K.S.
Continuous, measurement of BRSI in chronic fatigue syndrome

2004 Annual International Conference of the IEEE Engineering in Medicine and Biology – Proceedings 26 (II); 906 – 908

<http://www.scopus.com/inward/record.url?eid=2-s2.0-11144319904&partnerID=40>

New Jersey Institute of Technology, Newark; Eng. Technol. and Biomed. Eng., NJIT; Biomedical Engineering, NJIT; Univ. of Med. and Dent. New Jersey

This paper discusses the development of a system to measure continuous cardiac baroreceptor measurement during a 45-minute 70-degree head-up tilt (HUT) of five groups of subjects suffering the following: chronic fatigue syndrome (CFS), CFS with fibromyalgia (CFS-FM), CFS with postural orthostatic tachycardia syndrome (CFS-POTS), controls with POTS (CON-POTS), and controls (CON). The duration of the test was 56-minutes, which included a five-minute supine baseline, a 45-minute HUT and a six-minute recovery period. The system was developed in LabView, and can provide a comparative time analyses of weighted BRSI averages. Baroreflex effectiveness index (BEI) was also investigated over the course of lags 0, 1 and 2 as well as an assessment of overall BEI performance between groups.

Donnelly D.L., Rockland R.H., Reisman S.S., Quigley K.S.
Baroreflex sensitivity index in chronic fatigue syndrome

2004 Bioengineering, Proceedings of the Northeast Conference 30; 85 – 86
<http://www.scopus.com/inward/record.url?eid=2-s2.0-2942530751&partnerID=40>

New Jersey Institute of Technology, Newark; Eng. Technol. and Biomed. Eng.; Biomedical Engineering, NJIT; Univ. of Med./Dentistry New Jersey

This paper provides a graphical evaluation of continuous cardiac baroreceptor measurement during a 45-minute 70-degree head-up tilt (HUT) of five groups of subjects suffering the following: chronic fatigue syndrome (CFS), CFS with fibromyalgia (CFS-FM), CFS with postural orthostatic tachycardia syndrome (CFS-POTS), controls with POTS (CON-POTS), and controls (CON). The full duration of the test was 56-minutes, and included supine five-minute baseline and six-minute recovery periods. A comparative time analyses of weighted BRSI averages as well as the combined total number of sequences and ramps for lags 0, 1 and 2 is presented.

Burnet R.B., Chatterton B.E.
Gastric emptying is slow in chronic fatigue syndrome

2004 BMC Gastroenterology 4
<http://www.scopus.com/inward/record.url?eid=2-s2.0-25444434103&partnerID=40>

Department of Endocrinology and Metabolism, Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia; Department of Nuclear Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia

Background: Gastrointestinal symptoms are common in patients with Chronic Fatigue Syndrome (CFS). The objective of this study was to determine the frequency of these symptoms and explore their relationship with objective (radionuclide) studies of upper GI function. Methods: Thirty-two (32) patients with CFS and 45 control subjects completed a questionnaire on upper GI symptoms, and the 32 patients underwent oesophageal clearance, and simultaneous liquid and solid gastric emptying studies using radionuclide techniques compared with historical controls. Results: The questionnaires showed a significant difference in gastric ($p > 0.01$) symptoms and swallowing difficulty. Nocturnal diarrhoea was a significant symptom not previously reported. 5/32 CFS subjects showed slightly delayed oesophageal clearance, but overall there was no significant difference from the control subjects, nor correlation of oesophageal clearance with symptoms. 23/32 patients showed a delay in liquid gastric emptying, and 12/32 a delay in solid gastric emptying with the delay significantly correlated with the mean symptom score (for each $p < 0.001$). Conclusions: GI symptoms in patients with chronic fatigue syndrome are associated with objective changes of upper GI motility. © 2004 Burnet and Chatterton; licensee BioMed Central Ltd.

Tak L.M., Riese H., de Bock G.H., Manoharan A., Kok I.C., Rosmalen J.G.M.
As good as it gets? A meta-analysis and systematic review of methodological quality of heart rate variability studies in functional somatic disorders

Biological Psychology
<http://www.scopus.com/inward/record.url?eid=2-s2.0-66749139724&partnerID=40>

Interdisciplinary Center for Psychiatric Epidemiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB, Groningen, The Netherlands; Unit of Genetic Epidemiology and Bioinformatics, Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; Department of Biostatistics and Computing, Institute of Psychiatry, King's College London, London, United Kingdom

Autonomic nervous system (ANS) dysfunction is a potential mechanism connecting psychosocial stress to functional somatic disorders (FSD), such as chronic fatigue syndrome, fibromyalgia and irritable bowel syndrome. We present the first meta-analysis and systematic review of methodological study quality on the association between cardiac ANS dysfunction, measured as parasympathetic nervous system (PNS) activity using heart rate variability (HRV), and FSD. Literature search revealed 23

available studies including data on 533 FSD patients. Meta-analysis on a subgroup of 14 studies with suitable outcome measures indicated lower PNS activity in FSD patients compared to controls (weighted standardized mean difference (SMD) = -0.32, 95% CI -0.63 to -0.01, $p = 0.04$). The reliability of this summary estimate was, however, significantly limited by unexplained heterogeneity in the effect sizes and potential publication bias (weighted SMD after correction for funnel plot asymmetry = 0.01, 95% CI -0.34 to 0.36, $p = 0.95$). The systematic review of overall methodological quality of HRV studies in FSD demonstrates that there is substantial room for improvement, especially in selection of healthy control subjects, blinding of researchers performing HRV measurements, report of adequate HRV outcomes, and assessment of and adjustment for potential confounders. Methodological study quality was, however, not a significant predictor of study findings. We conclude that current available evidence is not adequate to firmly reject or accept a role of ANS dysfunction in FSD. Quality criteria and recommendations to improve future research on HRV in FSD are provided. © 2009 Elsevier B.V. All rights reserved.

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Does hypothalamic-pituitary-adrenal axis hypofunction in chronic fatigue syndrome reflect a 'crash' in the stress system?

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Abstract

The etiopathogenesis of chronic fatigue syndrome (CFS) remains poorly understood. Although neuroendocrine disturbances - and hypothalamic-pituitary-adrenal (HPA) axis hypofunction in particular - have been found in a large proportion of CFS patients, it is not clear whether these disturbances are cause or

consequence of the illness. After a review of the available evidence we hypothesize that that HPA axis hypofunction in CFS, conceptualized within a system-biological perspective, primarily reflects a fundamental and persistent dysregulation of the neurobiological stress system. As a result, a disturbed balance between glucocorticoid and inflammatory signaling pathways may give rise to a pathological cytokine-induced sickness response that may be the final common pathway underlying central CFS symptoms, i.e. effort/stress intolerance and pain hypersensitivity. This comprehensive hypothesis on HPA axis hypofunction in CFS may stimulate diagnostic refinement of the illness, inform treatment approaches and suggest directions for future research, particularly focusing on the neuroendocrine-immune interface and possible links between CFS, early and recent life stress, and depression. © 2009 Elsevier Ltd. All rights reserved.

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Epidemiology and Phenotyping

Hadlandsmyth K., Vowles K.E.

Does depression mediate the relation between fatigue severity and disability in chronic fatigue syndrome sufferers?

2009 Journal of Psychosomatic Research 66 (1); 31-35

<http://www.scopus.com/inward/record.url?eid=2-s2.0-57349178964&partnerID=40>

Bath and Wiltshire Adult Chronic Fatigue Syndrome Service, Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom; Centre for Pain Research, School for Health, University of Bath, Bath, United Kingdom

Objective: Chronic fatigue syndrome (CFS) is often associated with significant levels of disability. Although fatigue and depression have been found to be independently related to severity of disability, it is not clear how these three factors are mutually related. The present study sought to address this issue by specifically testing a model of mediation whereby depression was hypothesized to influence relations between fatigue and disability. Methods: Participants included 90 individuals seeking treatment for CFS at a tertiary care facility. Each provided demographic information and completed standardized measures of depression and fatigue severity, as well as a measure of disability, which assessed difficulties in physical, psychosocial, and independence domains. Results: Analyses indicated that depression and fatigue were positively correlated with one another, as well as all three disability domains. Analyses of mediation indicated that depression completely mediated the relation between fatigue and psychosocial disability and partially mediated the relation between fatigue and the other two disability domains. Indirect effects tests indicated that the inclusion of depression in the statistical models was statistically meaningful. Conclusions: These results replicate previous findings that fatigue and depression are independently related to disability in those with CFS. A more complex statistical model, however, suggested that depression severity substantially influenced the strength of the relation between fatigue and disability levels across a range of domains, including complete mediation in areas involving psychosocial functioning. These results may aid in clarifying contemporary conceptualizations of CFS and provide guidance in the identification of appropriate treatment targets. Â© 2009 Elsevier Inc. All rights reserved.

Van Houdenhove B., Van Hoof E., Becq K., Kempke S., Luyten P., De Meirleir K.

A comparison of patients with chronic fatigue syndrome in two "ideologically" contrasting clinics

2009 Journal of Nervous and Mental Disease 197 (5); 348 – 353

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67649399265&partnerID=40>

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Aim of the present study was to compare chronic fatigue syndrome (CFS) patients, attending 2 "ideologically" contrasting clinics for CFS, on various patient and illness characteristics. Fifty-nine CFS patients of each clinic, located in Leuven and Brussels (Belgium), participated. Patients did not differ with regard to age, levels of fatigue, psychopathology, and self-efficacy. However, patients from the psychosocially-oriented clinic had a lower level of education, reported more progressive illness onset, and attributed their illness more to psychological causes. Patients in the biologically-oriented clinic reported more pain, and showed higher levels of social functioning, motivation and vitality, as well as fewer limitations related to emotional problems. It is concluded that CFS patients attending the 2 clinics could not be distinguished along dualistic biological/psychosocial lines, but those reporting sudden illness onset and making somatic attributions were more likely to be represented in the biologically-oriented clinic. Â© 2009 by Lippincott Williams & Wilkins.

Kato K., Sullivan P.F., Evengard B., Pedersen N.L.
A population-based twin study of functional somatic syndromes.

2009 Psychological medicine 39 (3); 497 – 505

<http://www.scopus.com/inward/record.url?eid=2-s2.0-66149166219&partnerID=40>

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BACKGROUND: The mechanisms underlying the co-occurrence of the functional somatic syndromes are largely unknown. No empirical study has explicitly examined how genetic and environmental factors influence the co-morbidity of these syndromes. We aimed to examine how the co-morbidity of functional somatic syndromes is influenced by genetic and environmental factors that are in common to the syndromes. **METHOD:** A total of 31318 twins in the Swedish Twin Registry aged 41-64 years underwent screening interviews via a computer-assisted telephone system from 1998 to 2002. Four functional somatic syndromes (chronic widespread pain, chronic fatigue, irritable bowel syndrome, and recurrent headache) and two psychiatric disorders (major depression and generalized anxiety disorder) were assessed using structured questions based on standard criteria for each illness in a blinded manner. **RESULTS:** Multivariate twin analyses revealed that a common pathway model with two latent traits that were shared by the six illnesses fit best to the women's data. One of the two latent traits loaded heavily on the psychiatric disorders, whereas the other trait loaded on all four of the functional somatic syndromes, particularly chronic widespread pain, but not on the psychiatric disorders. All illnesses except the psychiatric disorders were also affected by genetic influences that were specific to each. **CONCLUSIONS:** The co-occurrence of functional somatic syndromes in women can be best explained by affective and sensory components in common to all these syndromes, as well as by unique influences specific to each of them. The findings clearly suggest a complex view of the multifactorial pathogenesis of these illnesses.

Hickie I., Davenport T., Vernon S.D., Nisenbaum R., Reeves W.C., Hadzi-Pavlovic D., Lloyd A.
Are chronic fatigue and chronic fatigue syndrome valid clinical entities across countries and healthcare settings?

2009 Australian and New Zealand Journal of Psychiatry 43 (1); 25 – 35

<http://www.scopus.com/inward/record.url?eid=2-s2.0-58049102313&partnerID=40>

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Objective: The validity of the diagnosis of chronic fatigue syndrome and related chronic fatigue states remains controversial, particularly in psychiatry. This project utilized international epidemiological and clinical research data to test construct validity across diagnostic categories, health-care settings and countries. Relevant demographic, symptom and diagnostic data were obtained from 33 studies in 21 countries. The subjects had fatigue lasting 1-6 months (prolonged fatigue), or >6 months (chronic fatigue), or met diagnostic criteria for chronic fatigue syndrome. **Method:** Common symptom domains were derived by factor analytic techniques. Mean scores on each symptom factor were compared across diagnostic categories, health-care settings and countries. **Results:** Data were obtained on 37 724 subjects (n = 20 845 female, 57%), including from population-based studies (n = 15 749, 42%), studies in primary care (n = 19 472, 52%), and secondary or specialist tertiary referral clinics (n = 2503, 7%). The sample included 2013 subjects with chronic fatigue, and 1958 with chronic fatigue syndrome. A five-factor model of the key symptom domains was preferred ('musculoskeletal pain/fatigue', 'neurocognitive difficulties', 'inflammation', 'sleep disturbance/fatigue' and 'mood disturbance') and was comparable across subject groups and settings. Although the core symptom profiles were similar, some differences in symptoms were observed across diagnostic categories, health-care settings and between countries. **Conclusions:** The construct validity of chronic fatigue and chronic fatigue syndrome is supported by an empirically derived factor structure from existing international datasets.

Hamilton W.T., Gallagher A.M., Thomas J.M., White P.D.

Risk markers for both chronic fatigue and irritable bowel syndromes: a prospective case-control study in primary care

2009 Psychological Medicine 1 (9)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-64249144226&partnerID=40>

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BACKGROUND: Fatigue syndromes and irritable bowel syndrome (IBS) often occur together. Explanations include being different manifestations of the same condition and simply sharing some symptoms. **METHOD:** A matched case-control study in UK primary care, using data collected prospectively in the General Practice Research Database (GPRD). The main outcome measures were: health-care utilization, specific symptoms and diagnoses. Risk markers were divided into distant (from 3 years to 1 year before diagnosis) and recent (1 year before diagnosis). **RESULTS:** A total of 4388 patients with any fatigue syndrome were matched to two groups of patients: those attending for IBS and those attending for another reason. Infections were specific risk markers for both syndromes, with viral infections being a risk marker for a fatigue syndrome [odds ratios (ORs) 2.3-6.3], with a higher risk closer to onset, and gastroenteritis a risk for IBS (OR 1.47, compared to a fatigue syndrome). Chronic fatigue syndrome (CFS) shared more distant risk markers with IBS than other fatigue syndromes, particularly other symptom-based disorders (OR 3.8) and depressive disorders (OR 2.3), but depressive disorders were a greater risk for CFS than IBS (OR 2.4). Viral infections were more of a recent risk marker for CFS compared to IBS (OR 2.8), with gastroenteritis a greater risk for IBS (OR 2.4). **CONCLUSIONS:** Both fatigue and irritable bowel syndromes share predisposing risk markers, but triggering risk markers differ. Fatigue syndromes are heterogeneous, with CFS sharing predisposing risks with IBS, suggesting a common predisposing pathophysiology.

Goudsmit E.M., Stouten B., Howes S.

Illness intrusiveness in myalgic encephalomyelitis: An exploratory study

2009 Journal of Health Psychology 14 (2); 215 – 221

<http://www.scopus.com/inward/record.url?eid=2-s2.0-60849089943&partnerID=40>

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This study assessed the relationship between illness intrusiveness, symptoms, disability and depression in patients with myalgic encephalomyelitis (ME). Participants were 16 patients with ME and eight patients with ME plus co-morbid disorders. The patients with co-morbid disorders reported greater illness intrusiveness than the patients with ME alone, but there were no differences between the groups on the other variables. Significant correlations were found between illness intrusiveness on the one hand, and fatigue, cognitive dysfunction, disability and depression, on the other. We conclude that ME is a disabling illness, which has a major impact on various life domains. Copyright © 2009 SAGE Publications.

Goedendorp M.M., Knoop H., Schippers G.M., Bleijenberg G.

The lifestyle of patients with chronic fatigue syndrome and the effect on fatigue and functional impairments

2009 Journal of Human Nutrition and Dietetics 22 (3); 226 – 231

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65649096534&partnerID=40>

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Background: Little is known about the lifestyle of patients with chronic fatigue syndrome (CFS) and its influence on symptoms of CFS. The present study aimed to investigate the lifestyle of patients with CFS, and to assess whether lifestyle factors are related to fatigue and functional impairments. Methods: Two hundred and forty-seven patients fulfilling the Center for Disease Control criteria for CFS were included. Validated questionnaires were used to collect data on lifestyle factors, smoking, intake of alcohol, fat, fibres, fruit and vegetables, body mass index (BMI), fatigue severity and functional impairments. Results: Of the CFS patients, 23% smoked, 32% had an unhealthy BMI, and none had an unhealthy alcohol intake. A majority had an unhealthy food intake: 70% had unhealthy fat, fruit and vegetable intake, and 95% had unhealthy fibre intake. Compared with the general Dutch population, significantly fewer CFS patients were overweight. Significantly more female CFS patients abstained from alcohol, and fewer male CFS patients smoked. Unhealthy lifestyle factors were not significantly associated with fatigue severity or functional impairments. Conclusions: CFS patients tend to lead a healthier lifestyle compared to the general Dutch population. However, no relationship was found between lifestyle factors and fatigue severity and functional impairments in CFS. © 2009 The British Dietetic Association.

Cho H.J., Menezes P.R., Hotopf M., Bhugra D., Wessely S.
Comparative epidemiology of chronic fatigue syndrome in Brazilian and British primary care: Prevalence and recognition

2009 British Journal of Psychiatry 194 (2); 117 – 122

<http://www.scopus.com/inward/record.url?eid=2-s2.0-60149098608&partnerID=40>

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Background Although fatigue is a ubiquitous symptom across countries, clinical descriptions of chronic fatigue syndrome have arisen from a limited number of high-income countries. This might reflect differences in true prevalence or clinical recognition influenced by sociocultural factors. Aims To compare the prevalence, physician recognition and diagnosis of chronic fatigue syndrome in London and Sao Paulo. Method Primary care patients in London (n=2459) and Sao Paulo (n=3914) were surveyed for the prevalence of chronic fatigue syndrome. Medical records were reviewed for the physician recognition and diagnosis. Results The prevalence of chronic fatigue syndrome according to Centers for Disease Control 1994 criteria was comparable in Britain and Brazil: 2.1% v. 1.6% (P=0.20). Medical records review identified 11 diagnosed cases of chronic fatigue syndrome in Britain, but none in Brazil (P<0.001). Conclusions The primary care prevalence of chronic fatigue syndrome was similar in two culturally and economically distinct nations. However, doctors are unlikely to recognise and label chronic fatigue syndrome as a discrete disorder in Brazil. The recognition of this illness rather than the illness itself may be culturally induced.

Nijrolder I., Van Der Windt D.A.W.M., Van Der Horst H.E.
Prognosis of fatigue and functioning in primary care: A 1-year follow-up study

2008 Annals of Family Medicine 6 (6); 519 – 527

<http://www.scopus.com/inward/record.url?eid=2-s2.0-56649092749&partnerID=40>

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PURPOSE: Although fatigue is a common presenting symptom in primary care and its course and outcomes often remain unclear, cohort studies among patients seeking care for fatigue are scarce. We therefore aimed to investigate patterns in the course of fatigue and relevant secondary outcomes in a large cohort of patients who sought care for a main symptom of fatigue. **METHODS:** We performed an observational cohort study in 147 primary care practices. Patients consulting their general practitioner for a new episode of fatigue were sent questionnaires at 1, 4, 8, and 12 months after baseline. We collected measures of fatigue, perceived health and functioning, absenteeism, psychological symptoms, and sleep using the Checklist Individual Strength, the 36-Item Short Form Health Survey, the Four-Dimensional Symptoms Questionnaire, and the Pittsburgh Sleep Questionnaire Inventory. Patients were classified into 4 subgroups based on fatigue severity scores over time. We assessed patterns in the course of all outcomes in these subgroups and in the total population, and tested changes over time and differences between subgroups. **RESULTS:** A total of 642 patients were enrolled in the study. Response rates during follow-up ranged between 82% and 88%. For 75% of the patients, 4 distinct groups could be discerned: 26% of patients had continuously high scores for fatigue, 17% had a fast recovery, 25% had a slow recovery, and 32% initially improved but then had a recurrence of fatigue. Patterns for the secondary outcomes of symptoms and functioning were all similar to the pattern for fatigue within each of the subgroups. **CONCLUSIONS:** The findings of this study suggest a longitudinal relationship between the severity of fatigue, impaired functioning, psychological symptoms, and poor sleep. Physicians should be aware that a substantial proportion of patients seeking care for fatigue have these additional health and psychosocial problems.

Hoad A., Spickett G., Elliott J., Newton J.

Postural orthostatic tachycardia syndrome is an under-recognized condition in chronic fatigue syndrome

2008 QJM 101 (12); 961 – 965

<http://www.scopus.com/inward/record.url?eid=2-s2.0-57049132672&partnerID=40>

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Background: It has been suggested that postural orthostatic tachycardia syndrome (POTS) be considered in the differential diagnosis of those with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Currently, measurement of haemodynamic response to standing is not recommended in the UK NICE CFS/ME guidelines. **Objectives:** To determine prevalence of POTS in patients with CFS/ME. **Design:** Observational cohort study. **Methods:** Fifty-nine patients with CFS/ME (Fukuda criteria) and 52 age- and sex-matched controls underwent formal autonomic assessment in the cardiovascular laboratory with continuous heart rate and beat-to-beat blood pressure measurement (Task Force, CNSystems, Graz Austria). Haemodynamic responses to standing over 2 min were measured. POTS was defined as symptoms of orthostatic intolerance associated with an increase in heart rate from the supine to upright position of >30 beats per minute or to a heart rate of >120 beats per minute on standing. **Results:** Maximum heart rate on standing was significantly higher in the CFS/ME group compared with controls (106 Å± 20 vs. 98 Å± 13; P = 0.02). Of the CFS/ME group, 27% (16/59) had POTS compared with 9% (5) in the control population (P = 0.006). This difference was predominantly related to the increased proportion of those in the CFS/ME group whose heart rate increased to >120 beats per minute on standing (P = 0.0002). Increasing fatigue was associated with increase in heart rate (P = 0.04; r² = 0.1). **Conclusions:** POTS is a frequent finding in patients with CFS/ME. We suggest that clinical evaluation of patients with CFS/ME should include response to standing. Studies are needed to determine the optimum intervention strategy to manage POTS in those with CFS/ME. Å© The Author 2008. Published by Oxford University Press on behalf of the Association of Physicians. All rights reserved.

Ciccione D.S., Weissman L., Natelson B.H.

Chronic fatigue syndrome in male Gulf War veterans and civilians: A further test of the single syndrome hypothesis

2008 *Journal of Health Psychology* 13 (4); 529 – 536

<http://www.scopus.com/inward/record.url?eid=2-s2.0-42149187643&partnerID=40>

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Different modes of fatigue onset in male Gulf War veterans versus male civilians raise the possibility that chronic fatigue syndrome (CFS) may not be a single disease entity. We addressed this issue by comparing 45 male veterans with CFS to 84 male civilians who satisfied identical case criteria. All were evaluated for fibromyalgia (FM), multiple chemical sensitivity and psychiatric comorbidity. CFS was more likely to present in a sudden flu-like manner in civilians than veterans ($p < .01$) and comorbid FM was more prevalent in civilians ($p < .01$). These findings question the assumption that all patients with CFS suffer from the same underlying disorder. Copyright © 2008 SAGE Publications.

Torres-Harding S.R., Mason-Shutter J., Jason L.A.

Fatigue among Spanish- and English-speaking Latinos.

2008 *Social work in public health* 23 (5); 55 – 72

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65349176468&partnerID=40>

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The present study investigated sociodemographic differences, fatigue severity, and the occurrence of prolonged or chronic fatigue reported by Spanish-speaking and English-speaking Latinos. The sample included 2,102 English-speaking Latinos and 1,348 Spanish-speaking Latinos interviewed as part of an epidemiological study of persons with chronic fatigue syndrome in the Chicago area. Results indicated that English-speaking Latinos scored higher on measure of fatigue than Spanish-speaking Latinos. Further, language status continued to be a predictor of fatigue level even when controlling for other sociodemographic differences found between the groups. Findings suggest that language spoken in Latino populations is important in predicting fatigue, and point to the potential importance of cultural factors such as acculturation or acculturative stresses.

Osoba T., Pheby D., Gray S., Nacul L.

The development of an epidemiological definition for myalgic encephalomyelitis/chronic fatigue syndrome

2008 *Journal of Chronic Fatigue Syndrome* 14 (4); 61 – 84

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650286464&partnerID=40>

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An epidemiological case-definition was developed to distinguish myalgic encephalomyelitis/chronic fatigue syndrome from other chronic fatiguing conditions by evaluating the discriminatory potential of different criteria from previous definitions. A two-part model was derived using consensus and discriminant analytic approaches. The optimal discriminators for the first part were severe debilitating fatigue affecting physical and mental functioning, a reduction in activity to less than 50% of the patient's premorbid activity level, and muscle discomfort (sensitivity 92%, specificity 66%). The variables for the second part included a reduction in activity to less than 50% of the patient's premorbid activity, myalgia, generalized muscle weakness, migratory arthralgia, and swollen lymph nodes (sensitivity 77%, specificity 88%). © 2008 by Informa Healthcare USA, Inc.

Kim S.-H.

Prevalence of chronic widespread pain and chronic fatigue syndrome in young Korean adults

2008 *Journal of Musculoskeletal Pain* 16 (3); 149 – 153

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650329838&partnerID=40>

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Objectives: There have been many epidemiological studies on chronic widespread pain [CWP] and chronic fatigue syndrome [CFS] in the general population or samples ascertained from clinical sources, but such studies have not been reported in similarly aged young people. It may be helpful to report in which homogenous group CWP and CFS are more prevalent for future research about the pathogenesis of these illnesses. This study was conducted to estimate the prevalence of CWP and CFS in Korean university freshmen. Methods: Those who participated in the freshmen orientation of a large Korean university in March 2006 were evaluated for the prevalence of CWP and CFS. Interviews were conducted by trained personnel with adequate medical background using a questionnaire that included demographic characteristics, smoking, CWP, and fatigue. Results: Among the 1,644 freshmen interviewed, 815 participants [49.6%] were men and 829 participants [50.4%] were women. There were five cases of CWP [0.3%]; three of the cases were men and two were women. The CFS was detected in only one male case [0.06 percent]. Conclusion: The prevalence of CWP was 0.3%, which was much lower than statistics [7.3 to 14.0%] reported by previous studies of the general population. It would seem useful to investigate the prevalence of CWP and CFS according to age to facilitate further study of the aging factors in the pathogenesis of CWP and CFS. © 2008 by Informa Healthcare USA, Inc.

Kara I.H., Demir D., Erdem O., Sayin G.T., Yildiz N., Yaman H.

Chronic fatigue syndrome among nurses and healthcare workers in a research hospital in Turkey

2008 *Social Behavior and Personality* 36 (5); 585 – 590

<http://www.scopus.com/inward/record.url?eid=2-s2.0-53149142501&partnerID=40>

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Chronic fatigue syndrome (CFS) among nurses and healthcare workers was evaluated via a questionnaire examining CFS, sociodemographic factors, lifestyle, work capacity and education. The criteria of the Centers for Disease Control were applied. One hundred and eighty-three nurses and 18 healthcare workers (mean age 29.04 ± 5.31 years) participated. More than half of cases (n = 116, 57.7%) complained of fatigue. Thirty-six cases (17.9%) fully matched the criteria of the CDC for CFS. High income level (> \$400/month) (p = 0.005) and overworking (> 8 hr/day) (p = 0.017) had a significant effect on CFS [high income (OR: 9.60, CI, 95%: 1.98 - 46.54) and overworking (OR: 7.66, CI, 95%: 1.44 - 40.92), respectively]. CFS was also related to being under 35 years old.

Ismail K., Kent K., Sherwood R., Hull L., Seed P., David A.S., Wessely S.

Chronic fatigue syndrome and related disorders in UK veterans of the Gulf War 1990-1991: Results from a two-phase cohort study

2008 *Psychological Medicine* 38 (7); 953 – 961

<http://www.scopus.com/inward/record.url?eid=2-s2.0-44449102169&partnerID=40>

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Background. The aim was to determine the prevalence of chronic fatigue syndrome (CFS), chronic fatigue and fibromyalgia in UK military personnel after the Gulf War 1990-1991. **Method.** A two-phase cohort study was used. Three randomly selected subsamples identified from a population-based cross-sectional postal survey of over 10 000 current and ex-service UK military personnel (Gulf veterans were those deployed to the Gulf War 1990-1991; non-Gulf veterans were Bosnia peacekeepers 1992-1997 and those on active duty during the Gulf War 1990-1991 but not deployed) were recruited. Their disability status was assessed using the Short Form 36 physical functioning scale; Gulf veterans who reported physical disability (n=111) were compared with non-Gulf (n=133) veterans who reported similar levels of physical disability. Screening for known medical and psychiatric conditions was conducted to exclude medical explanations for disability and symptomatic distress. Standardised criteria for CFS, chronic fatigue and fibromyalgia were used. **Results:** Disabled Gulf veterans were more likely to be overweight, have elevated Γ^3 -glutamyl transferase levels and screen positive for hypertension. There were no other clinically significant differences in clinical markers for medically explainable conditions. Disabled Gulf veterans were more likely than similarly disabled Bosnia and Era veterans (adjusted odds ratio 7.8, 95% confidence interval 2.5-24.5) to meet the criteria for CFS. Rates for other medically unexplained conditions were not significantly increased. **Conclusions:** Symptoms in keeping with CFS account for a significant part of the symptomatic distress in Gulf veterans. Copyright © 2007 Cambridge University Press.

Davies S., Crawley E.

Chronic fatigue syndrome in children aged 11 years old and younger

2008 Archives of Disease in Childhood 93 (5); 419 – 422

<http://www.scopus.com/inward/record.url?eid=2-s2.0-44349136246&partnerID=40>

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Children in primary school can be very disabled by chronic fatigue syndrome or ME (CFS/ME). The clinical presentation in this age group (under 12 years old) is almost identical to that in older children. **Aim:** To describe children who presented to the Bath paediatric CFS/ME service under the age of 12 years. **Method:** Inventories measuring fatigue, pain, functional disability, anxiety, family history and symptoms were collected prospectively for all children presenting to the Bath CFS/ME service between September 2004 and April 2007. Data from children who presented to the service under the age of 12 are described and compared to those who presented at age 12 or older. **Results:** 178 children (under the age of 18) were diagnosed as having CFS/ME using the RCPCH criteria out of 216 children assessed. The mean age at assessment for children with CFS/ME was 14.5 years old (SD 2.9). Thirty-two (16%) children were under 12 years at the time of assessment, four children were under 5 years and the youngest child was 2 years old. Children under 12 were very disabled with mean school attendance of just over 40% (average 2 days a week), Chalder fatigue score of 8.29 (CI 7.14 to 9.43 maximum possible score = 11) and pain visual analogue score of 39.7 (possible range 0-100). Comparison with children aged 12 or older showed that both groups were remarkably similar at assessment. Twenty-four out of the 26 children with complete symptom lists would have been diagnosed as having CFS/ME using the stricter adult Centers of Disease Control and prevention (CDC) criteria. **Conclusion:** Disability in the under-12 age group was high, with low levels of school attendance, high levels of fatigue, anxiety, functional disability and pain. The clinical pattern seen is almost identical to that seen in older children, and the majority of children would also be diagnosed as having CFS/ME using the stricter adult definition.

Bhattacharjee M., Botting C.H., Sillanpaa M.J.

Bayesian biomarker identification based on marker-expression proteomics data

2008 Genomics 92 (6); 384 – 392

<http://www.scopus.com/inward/record.url?eid=2-s2.0-55949098380&partnerID=40>

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We are studying variable selection in multiple regression models in which molecular markers and/or gene-expression measurements as well as intensity measurements from protein spectra serve as predictors for the outcome variable (i.e., trait or disease state). Finding genetic biomarkers and searching genetic-epidemiological factors can be formulated as a statistical problem of variable selection, in which, from a large set of candidates, a small number of trait-associated predictors are identified. We illustrate our approach by analyzing the data available for chronic fatigue syndrome (CFS). CFS is a complex disease from several aspects, e.g., it is difficult to diagnose and difficult to quantify. To identify biomarkers we used microarray data and SELDI-TOF-based proteomics data. We also analyzed genetic marker information for a large number of SNPs for an overlapping set of individuals. The objectives of the analyses were to identify markers specific to fatigue that are also possibly exclusive to CFS. The use of such models can be motivated, for example, by the search for new biomarkers for the diagnosis and prognosis of cancer and measures of response to therapy. Generally, for this we use Bayesian hierarchical modeling and Markov Chain Monte Carlo computation. © 2008 Elsevier Inc. All rights reserved.

Schur E.A., Afari N., Furberg H., Olarte M., Goldberg J., Sullivan P.F., Buchwald D.

Feeling bad in more ways than one: Comorbidity patterns of medically unexplained and psychiatric conditions

2007 Journal of General Internal Medicine 22 (6); 818 – 821

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34248547351&partnerID=40>

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BACKGROUND: Considerable overlap in symptoms and disease comorbidity has been noted among medically unexplained and psychiatric conditions seen in the primary care setting, such as chronic fatigue syndrome, low back pain, irritable bowel syndrome, chronic tension headache, fibromyalgia, temporomandibular joint disorder, major depression, panic attacks, and posttraumatic stress disorder. **OBJECTIVE:** To examine interrelationships among these 9 conditions. **DESIGN:** Using data from a cross-sectional survey, we described associations and used latent class analysis to investigate complex interrelationships. **PARTICIPANTS:** 3,982 twins from the University of Washington Twin Registry. **MEASUREMENTS:** Twins self-reported a doctor's diagnosis of the conditions. **RESULTS:** Comorbidity among these 9 conditions far exceeded chance expectations; 31 of 36 associations were significant. Latent class analysis yielded a 4-class solution. Class I (2% prevalence) had high frequencies of each of the 9 conditions. Class II (8% prevalence) had high proportions of multiple psychiatric diagnoses. Class III (17% prevalence) participants reported high proportions of depression, low back pain, and headache. Participants in class IV (73% prevalence) were generally healthy. Class I participants had the poorest markers of health status. **CONCLUSIONS:** These results support theories suggesting that medically unexplained conditions share a common etiology. Understanding patterns of comorbidity can help clinicians care for challenging patients. © 2007 Society of General Internal Medicine.

Van Den Bree M.B.M., Rice F., Fowler T.A., Shelton K.H., Lifford K.J., Scourfield J., Harold G.T., Thapar A.

The Cardiff Study of All Wales and North West of England Twins (CaStANET): A longitudinal research program of child and adolescent development

2007 Twin Research and Human Genetics 10 (1); 13 – 23

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33947207307&partnerID=40>

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The study of twins and their families provides a highly useful tool for disentangling the genetic and environmental origins of traits. The Cardiff Study of All Wales and North West of England Twins (CaStANET) has followed children and adolescents over time into early adulthood, assessing a wide range of aspects of behavior and psychopathology using self-, parent and teacher reports. Four main waves of data collection have taken place to date, which have provided a wealth of information on the contributions of genetic and environmental risk factors to the psychological health of young people. This article first describes the CaStANET register and subsequently presents some of the findings that have emerged from this resource, with a focus on depression and anxiety, chronic fatigue, attention-deficit/hyperactivity disorder, conduct problems and prosocial behavior. We describe in somewhat more detail the 4th wave of data collection, which has recently been completed and has provided us with extensive information on substance use and problem use as well as associated risk factors in the twins and their families, including longitudinal data on conduct problems and the relations between family members. Because of the wealth of data already collected and the opportunity for genetically informative analyses over time, CaStANET provides a valuable resource for understanding the complexities of the psychological development of young people.

Schur E., Afari N., Goldberg J., Buchwald D., Sullivan P.F.

Twin analyses of fatigue

2007 Twin Research and Human Genetics 10 (5); 729- 733

<http://www.scopus.com/inward/record.url?eid=2-s2.0-35349015123&partnerID=40>

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Prolonged fatigue equal to or greater than 1 month duration and chronic fatigue equal to or greater than 6 months duration are both commonly seen in clinical practice, yet little is known about the etiology or epidemiology of either symptom. Chronic fatigue syndrome (CFS), while rarer, presents similar challenges in determining cause and epidemiology. Twin studies can be useful in elucidating genetic and environmental influences on fatigue and CFS. The goal of this article was to use biometrical structural equation twin modeling to examine genetic and environmental influences on fatigue, and to investigate whether these influences varied by gender. A total of 1042 monozygotic (MZ) twin pairs and 828 dizygotic (DZ) twin pairs who had completed the University of Washington Twin Registry survey were assessed for three fatigue-related variables: prolonged fatigue, chronic fatigue, and CFS. Structural equation twin modeling was used to determine the relative contributions of additive genetic effects, shared environmental effects, and individual-specific environmental effects to the 3 fatigue conditions. In women, tetrachoric correlations were similar for MZ and DZ pairs for prolonged and chronic fatigue, but not for CFS. In men, however, the correlations for prolonged and chronic fatigue were higher in MZ pairs than in DZ pairs. About half the variance for both prolonged and chronic fatigue in males was due to genetic effects, and half due to individual-specific environmental effects. For females, most variance was due to individual environmental effects.

Rimes K.A., Goodman R., Hotopf M., Wessely S., Meltzer H., Chalder T.
Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: A prospective community study

2007 Pediatrics 119 (3)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33947114229&partnerID=40>

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OBJECTIVE. The objective of this study was to describe the incidence, prevalence, risk factors, and prognosis of fatigue, chronic fatigue, and chronic fatigue syndrome in 11- to 15-year-olds. **METHODS.** A random general population sample (n = 842) of British adolescents and their parents were assessed at baseline and 4 to 6 months later. The main outcomes were fatigue, chronic fatigue, and chronic fatigue syndrome, operationally defined. **RESULTS.** The incidence over 4 to 6 months was 30.3% for fatigue, 1.1% for chronic fatigue, and 0.5% for chronic fatigue syndrome. The point prevalence was 34.1% and 38.1% for fatigue, 0.4% and 1.1% for chronic fatigue, and 0.1% and 0.5% for chronic fatigue syndrome at time 1 and time 2, respectively. Of participants who were fatigued at time 1, 53% remained fatigued at time 2. The 3 cases of chronic fatigue and 1 case of chronic fatigue syndrome at time 1 had recovered by time 2. Higher risk for development of chronic fatigue at time 2 was associated with time 1 anxiety or depression, conduct disorder, and maternal distress; in multivariate analysis, baseline anxiety or depression remained a significant predictor of chronic fatigue. Increased risk for development of fatigue at time 2 was associated with time 1 anxiety or depression, conduct disorder, and older age; in multivariate analyses, these factors and female gender all were significant predictors of fatigue. **CONCLUSIONS.** The incidence rates for chronic fatigue and chronic fatigue syndrome in this adolescent sample were relatively high, but the prognosis for these conditions was good. This prospective study provides evidence for an association between emotional/behavioral problems and subsequent onset of fatigue/chronic fatigue. Copyright © 2007 by the American Academy of Pediatrics.

Reeves W.C., Jones J.F., Maloney E., Heim C., Hoaglin D.C., Boneva R.S., Morrissey M., Devlin R.
Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia

2007 Population Health Metrics 5

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34447315846&partnerID=40>

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Background: Chronic fatigue syndrome (CFS) is a debilitating illness with no known cause or effective therapy. Population-based epidemiologic data on CFS prevalence are critical to put CFS in a realistic context for public health officials and others responsible for allocating resources. **Methods:** Based on a random-digit dialing survey we ascertained CFS cases and controls to estimate the prevalence of CFS in metropolitan, urban, and rural populations of Georgia. This report focuses on the 5,623 of 19,381 respondents ages 18 to 59 years old. Fatigued (2,438), randomly selected unwell not fatigued (1,429) and randomly selected well (1,756) respondents completed telephone questionnaires concerning fatigue, other symptoms, and medical history. Subsets of those identified by interview as having CFS-like illness (292), chronic unwellness which was not CFS-like (268 - randomly selected), and well subjects (223, matched to those with CFS-like illness on sex, race, and age) completed a clinical evaluation. **Results:** We estimated that 2.54% of persons 18 to 59 years of age suffered from CFS. There were no significant differences in prevalence of CFS between metropolitan, urban or rural populations or between white and black residents of the three regions. However, there were significant

differences in female-to-male ratios of prevalence across the strata (metropolitan female: male 11.2 : 1, urban 1.7 : 1, rural 0.8 : 1). Conclusion: We estimated that 2.54% of the Georgia population suffers from CFS, which is 6- to 10-fold higher than previous population-based estimates in other geographic areas. These differences may reflect broader screening criteria and differences in the application of the case definition. However, we cannot exclude the possibility that CFS prevalence may be higher in Georgia than other areas where it has been measured. Although the study did not identify differences in overall prevalence between metropolitan, urban, and rural Georgia populations, it did suggest the need for additional stratified analyses by geographic strata. © 2007 Reeves et al; licensee BioMed Central Ltd.

Njoku M.G.C., Jason L.A., Torres-Harding S.R.
The prevalence of chronic fatigue syndrome in Nigeria

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-34047267672&partnerID=40>

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The present study found adult rates of chronic fatigue syndrome (CFS) in Nigeria that were somewhat higher than rates from community-based CFS epidemiologic studies in the USA. The rates of chronic fatigue for both adults and children were also higher than in existing community-based studies. It is possible that the presence of several fatiguing illnesses such as malaria and typhoid, the lack of adequate healthcare resources and poverty in Nigeria, place individuals at greater risk for fatigue and its syndromes. There is a need for more epidemiologic studies on the prevalence and sociodemographic characteristics of CFS in developing countries. Copyright © 2007 SAGE Publications.

Whistler T., Taylor R., Craddock R.C., Broderick G., Klimas N., Unger E.R.
Gene expression correlates of unexplained fatigue

2006 Pharmacogenomics 7 (3); 395 – 405

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646027897&partnerID=40>

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Quantitative trait analysis (QTA) can be used to test whether the expression of a particular gene significantly correlates with some ordinal variable. To limit the number of false discoveries in the gene list, a multivariate permutation test can also be performed. The purpose of this study is to identify peripheral blood gene expression correlates of fatigue using quantitative trait analysis on gene expression data from 20,000 genes and fatigue traits measured using the multidimensional fatigue inventory (MFI). A total of 839 genes were statistically associated with fatigue measures. These mapped to biological pathways such as oxidative phosphorylation, gluconeogenesis, lipid metabolism, and several signal transduction pathways. However, more than 50% are not functionally annotated or associated with identified pathways. There is some overlap with genes implicated in other studies using differential gene expression. However, QTA allows detection of alterations that may not reach statistical significance in class comparison analyses, but which could contribute to disease pathophysiology. This study supports the use of phenotypic measures of chronic fatigue syndrome (CFS) and QTA as important for additional studies of this complex illness. Gene expression correlates of other phenotypic measures in the CFS Computational Challenge (C3) data set could be useful. Future studies of CFS should include as many precise measures of disease phenotype as is practical. © 2006 Future Medicine Ltd.

Vollmer-Conna U., Aslakson E., White P.D.

An empirical delineation of the heterogeneity of chronic unexplained fatigue in women

2006 Pharmacogenomics 7 (3); 355 - 364

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646061666&partnerID=40>

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Objectives: To test the hypothesis that medically unexplained chronic fatigue and chronic fatigue syndrome (CFS) are heterogeneous conditions, and to define the different conditions using both symptom and laboratory data. Methods: We studied 159 women from KS, USA. A total of 51 of these suffered from fatigue consistent with established criteria for CFS, 55 had chronic fatigue of insufficient symptoms/severity for a CFS diagnosis and 53 were healthy controls matched by age and body mass index (BMI) against those with CFS. We used principal components analyses to define factors that best described the variable space and to reduce the number of variables. The 38 most explanatory variables were then used in latent class analyses to define discrete subject groups. Results: Principal components analyses defined six discrete factors that explained 40% of the variance. Latent class analyses provided several interpretable solutions with four, five and six classes. The four-class solution was statistically most convincing, but the six-class solution was more interpretable. Class 1 defined 41 (26%) subjects with obesity and relative sleep hypnoea. Class 2 were 38 (24%) healthy subjects. Class 3 captured 24 (15%) obese relatively hypnoeic subjects, but with low heart rate variability and cortisol. Class 4 were 23 (14%) sleep-disturbed and myalgic subjects without obesity or significant depression. The two remaining classes with 22 (14%) and 11 (7%) subjects consisted of the most symptomatic and depressed, but without obesity or hypnoea. Class 5 had normal sleep indices. Class 6 was characterized by disturbed sleep, with low sleep heart rate variability, cortisol, and sex hormones. Conclusion: Chronic medically unexplained fatigue is heterogeneous. The putative syndromes were differentiated by obesity, sleep hypnoea, depression, physiological stress response, sleep disturbance, interoception and menopausal status. If these syndromes are externally validated and replicated, they may prove useful in determining the causes, pathophysiology and treatments of CFS. © 2006 Future Medicine Ltd.

Janal M.N., Ciccone D.S., Natelson B.H.

Sub-typing CFS patients on the basis of 'minor' symptoms

2006 Biological Psychology 73 (2); 124 - 131

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33745949719&partnerID=40>

Fatigue Research Center, Department of Psychiatry, New Jersey Medical School, BHSB-F1522, Box 1709, Newark, NJ 07101, United States; Fatigue Research Center, Department of Neurosciences, New Jersey Medical School, Newark, NJ, United States

The diagnosis of chronic fatigue syndrome (CFS), an illness characterized by medically unexplained fatigue, depends on a clinical case definition representing one or more pathophysiological mechanisms. To prepare for studies of these mechanisms, this study sought to identify subtypes of CFS. In 161 women meeting 1994 criteria for CFS, principal components analysis of the 10 'minor' symptoms of CFS produced three factors interpreted to indicate musculoskeletal, infectious and neurological subtypes. Extreme scores on one or more of these factors characterized about 2/3 of the sample. Those characterized by the neurological factor were at increased risk of reduced scores on cognitive tests requiring attention, working memory, long-term memory or rapid performance. In addition, the neurological subtype was associated with reduced levels of function. Those characterized by the musculoskeletal factor were at increased risk for the diagnosis of fibromyalgia (chronic widespread pain and mechanical allodynia) and reduced physical function. Those characterized by the infectious factor were less likely to evidence co-occurring fibromyalgia, and showed lesser risk of functional impairment. The prevalence of disability was increased in those with the highest scores on any of the subtypes, as well as in those with high scores on multiple factors. Depression and anxiety, while frequently present, were not more prevalent in any particular subtype, and did not increase with the severity of specific

symptom reports. Results suggest that subtypes of CFS may be identified from reports of the minor diagnostic symptoms, and that these subtypes demonstrate construct validity. © 2006 Elsevier B.V. All rights reserved.

Hawk C., Jason L.A., Torres-Harding S.
Differential diagnosis of chronic fatigue syndrome and major depressive disorder

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The goal of this study was to identify variables that successfully differentiated patients with chronic fatigue syndrome, major depressive disorder, and controls. Fifteen participants were recruited for each of these three groups, and discriminant function analyses were conducted. Using symptom occurrence and severity data from the Fukuda et al. (1994) definitional criteria, the best predictors were postexertional malaise, unrefreshing sleep, and impaired memory-concentration. Symptom occurrence variables only correctly classified 84.4% of cases, whereas 91.1% were correctly classified when using symptom severity ratings. Finally, when using percentage of time fatigue reported, postexertional malaise severity, unrefreshing sleep severity, confusion-disorientation severity, shortness of breath severity, and self-reproach to predict group membership, 100% were classified correctly. Copyright © 2006 by Lawrence Erlbaum Associates, Inc.

Aslakson E., Vollmer-Conna U., White P.D.
The validity of an empirical delineation of heterogeneity in chronic unexplained fatigue

2006 Pharmacogenomics 7 (3); 365 - 373

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646039806&partnerID=40>

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Objectives: To validate a latent class structure derived empirically from a clinical data set obtained from persons with chronic medically unexplained fatigue. Methods: The strategies utilized in this validation study included: recalculating latent class analysis (LCA) results varying random seeds and the number of initial random starting sets; recalculating LCA results by substituting alternate variables to demonstrate a robust solution; determining the statistical significance of between-class differences on disability, fatigue and demographic measures omitted from the data set used for LCA; cross-classifying class membership using established Centers for Disease Control and Prevention (CDC) research criteria for chronic fatigue syndrome (CFS) to compare the relative proportions of subjects designated CFS, chronic fatigue (not CFS) or healthy controls captured by the latent classes. Results: Recalculation of results and substitution of variables for low-loading variables demonstrated a robust LCA result. Highly significant between-class differences were confirmed between Class 2 (well) and those interpreted as ill/fatigued. Analysis of between-class differences for the fatigue groups revealed significant differences for all disability and fatigue variables, but with equivalent levels of reported activity and reduction in motivation. Cross-classification against established CDC criteria demonstrated that 89% of subjects constituting Class 2 (well) were indeed nonfatigued controls. A general tendency for grouping CFS cases in the multiple symptomatic classes was noted. Conclusion: This study established reasonably good validity for an empirically-derived latent class solution reflecting considerable heterogeneity among subjects with medically unexplained chronic fatigue. This work strengthens the growing understanding of CFS as a heterogeneous entity comprised of several conditions with different underlying pathophysiological mechanisms. © 2006 Future Medicine Ltd.

Van De Putte E.M., Van Doornen L.J.P., Engelbert R.H.H., Kuis W., Kimpfen J.L.L., Uiterwaal C.S.P.M.
Mirrored symptoms in mother and child with chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33745319549&partnerID=40>

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OBJECTIVE. Our aim with this study was to assess the relation between chronic fatigue syndrome in adolescents and fatigue and associated symptoms in their fathers and mothers, more specifically the presence of chronic fatigue syndrome-like symptoms and psychologic distress. **METHOD.** In this cross-sectional study, 40 adolescents with chronic fatigue syndrome according to the Centers for Disease Control and Prevention criteria were compared with 36 healthy control subjects and their respective parents. Questionnaires regarding fatigue (Checklist Individual Strength), fatigue-associated symptoms, and psychopathology (Symptom Checklist-90) were applied to the children and their parents. **RESULTS.** Psychologic distress in the mother corresponds with an adjusted odds ratio of 5.6 for the presence of CFS in the child. The presence of fatigue in the mother and dimensional assessment of fatigue with the Checklist Individual Strength revealed odds ratios of, respectively, 5.29 and 2.86 for the presence of chronic fatigue syndrome in the child. An increase of 1 SD of the hours spent by the working mother outside the home reduced the risk for chronic fatigue syndrome in their child with 61%. The fathers did not show any risk indicator for chronic fatigue syndrome in their child. **CONCLUSIONS.** Mothers of adolescents with chronic fatigue syndrome exhibit fatigue and psychologic symptoms similar to their child in contrast with the fathers. The striking difference between the absent association in fathers and the evident association in mothers suggests that the shared symptom complex of mother and child is the result of an interplay between genetic vulnerability and environmental factors. Copyright © 2006 by the American Academy of Pediatrics.

Underhill R.A., O'Gorman R.

Prevalence of chronic fatigue syndrome and chronic fatigue within families of CFS patients

2006 *Journal of Chronic Fatigue Syndrome* 13 (1); 3 - 13

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33748574275&partnerID=40>

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The prevalence of CFS (Chronic Fatigue Syndrome) and chronic fatigue were investigated in family members of CFS patients using a questionnaire-based study. Significant differences were seen between the prevalence of CFS in all groups of family members relative to the published community prevalence of 0.422% (spouses/partners: 3.2%, $p < 0.001$; offspring: 5.1%, $p < .001$; parents and siblings: 1.1%, $p < 0.02$; second and third degree blood relatives 0.8%, $p < 0.02$). The prevalence of CFS was higher in genetically unrelated household contacts and in nonresident genetic relatives than in the community, indicating that both household contact and genetic relationship are risk factors for CFS. © 2006 by The Haworth Press, Inc. All rights reserved.

Ter Wolbeek M., Van Doornen L.J.P., Kavelaars A., Heijnen C.J.

Severe fatigue in adolescents: A common phenomenon?

2006 *Pediatrics* 117 (6)

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OBJECTIVE. The purpose of this study was to determine the prevalence of severe fatigue in adolescent boys and girls, to explore the role of lifestyle factors in fatigue, and to investigate whether severe fatigue in a healthy population is associated with depression, anxiety, and comorbid factors also observed in chronic fatigue syndrome patients. **METHODS.** In a sample of 1718 boys and 1749 girls, fatigue severity and duration were measured using a multidimensional questionnaire (Checklist Individual Strength). In addition, self-reports of depressive symptoms, anxiety, chronic fatigue syndrome-related symptoms, and lifestyle characteristics were assessed by means of questionnaires. Prevalence rates of severe fatigue and severe fatigue for ≥ 1 month, based on a clinical cutoff score of the Checklist Individual Strength, were determined for boys and girls separately, and gender-specific predictors of fatigue were identified by multiple regression analysis. **RESULTS.** The data showed high prevalence rates of severe fatigue in adolescents. Remarkable differences between boys and girls were observed: 20.5% of girls and 6.5% of the boys scored above the clinical cutoff score on the Checklist Individual Strength. Of these subjects 80.0% of the girls and 61.5% of the boys reported severe fatigue for ≥ 1 month. Of the examined lifestyle characteristics, only sleep characteristics and the participation in sports played a role in predicting fatigue in both genders. Moreover, in girls, fatigue was associated with higher age, an early menarche, medication use, and the absence of an additional job. Overall, girls scored higher on depression, anxiety, and chronic fatigue syndrome-related symptoms. However, the relation between fatigue and these comorbid symptoms did not differ between genders. In both girls and boys, the duration of fatigue was positively related to fatigue severity, severity of depression and anxiety, and the number of chronic fatigue syndrome-related symptoms. **CONCLUSIONS.** Fatigue prevalence among adolescents is high, especially in girls. Adolescent girls seem to be more vulnerable to symptoms of fatigue and comorbidity than boys. Interestingly, despite a female predominance in complaints, the relation between fatigue and depression, anxiety, and chronic fatigue syndrome-related symptoms was not gender specific and emerged as a cluster. In both genders, fatigue duration was associated with the severity of fatigue and the level of psychological comorbidity and chronic fatigue syndrome-related symptoms, and we, therefore, hypothesize that enduring severe fatigue may form a risk factor for the development of chronic fatigue syndrome. Copyright © 2006 by the American Academy of Pediatrics.

Jordan K.M., Jason L.A., Mears C.J., Katz B.Z., Rademaker A., Huang C.-F., Richman J., McCready W., Ayers P.M., Taylor K.K.

Prevalence of pediatric chronic fatigue syndrome in a community-based sample

2006 Journal of Chronic Fatigue Syndrome 13 (02-Mar); 75 – 78

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847365294&partnerID=40>

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Background: This study evaluated the prevalence of chronic fatigue syndrome (CFS) among children and adolescents (ages 5 to 17) in an ethnically and socioeconomically diverse community population. **Objectives:** This investigation attempted to address limitations of previous studies by using a community-based sample and thoroughly evaluating each participant (i.e., using medical and psychological evaluations) to determine a proper diagnosis of CFS. **Methods:** A community-based sample of children and adolescents aged 5 to 17 were screened for symptoms of chronic fatigue syndrome by telephone. Those reported to suffer from CFS-like symptoms were given medical and psychological evaluations to allow a determination of the CFS diagnosis. **Results:** The overall prevalence rate for the sample was 60 per 100,000 or .06%. The prevalence for the adolescents (aged 13 to 17)

was 181 per 100,000 or 181%. Conclusions: The current prevalence estimate for CFS in adolescents is higher than previous estimates. CFS was more common in adolescents than pre-pubescent children. © 2006 by The Haworth Press, Inc. All rights reserved.

Aggarwal V.R., McBeth J., Zakrzewska J.M., Lunt M., Macfarlane G.J.

The epidemiology of chronic syndromes that are frequently unexplained: Do they have common associated factors?

2006 International Journal of Epidemiology 35 (2); 468 – 476

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Background: Syndromes for which no physical or pathological changes can be found tend to be researched and managed in isolation although hypotheses suggest that they may be one entity. The objectives of our study were to investigate the co-occurrence, in the general population, of syndromes that are frequently unexplained and to evaluate whether they have common associated factors. Methods: We conducted a population-based cross-sectional survey that included 2299 subjects who were registered with a General Medical Practice in North-west England and who completed full postal questionnaires (response rate 72%). The study investigated four chronic syndromes that are frequently unexplained: chronic widespread pain, chronic oro-facial pain, irritable bowel syndrome, and chronic fatigue. Validated instruments were used to measure the occurrence of syndromes and to collect information on a variety of associated factors: demographic (age, gender), psychosocial (anxiety, depression, illness behaviour), life stressors, and reporting of somatic symptoms. Results: We found that 587 subjects (27%) reported one or more syndromes: 404 (18%) reported one, 134 (6%) reported two, 34 (2%) reported three, and 15 (1%) reported all four syndromes. The occurrence of multiple syndromes was greater than would be expected by chance ($P < 0.001$). There were factors that were common across syndromes: female gender [odds ratio (OR) = 1.8; 95% confidence interval (95% CI) 1.5-2.2], high levels of aspects of health anxiety like health worry preoccupation (OR = 3.5; 95% CI 2.8-4.4) and reassurance seeking behaviour (OR = 1.4; 95% CI 1.1-1.7), reporting of other somatic symptoms (OR = 3.6; 95% CI 2.9-4.4), and reporting of recent adverse life events (OR = 2.3; 95% CI 1.9-2.8). Conclusion: This study has shown that chronic syndromes that are frequently unexplained co-occur in the general population and share common associated factors. Primary care practitioners need to be aware of these characteristics so that management is appropriate at the outset. © 2006 Oxford University Press.

Lapp C.W.

Recognizing pediatric CFS in the primary care practice: A practicing clinician's approach

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847357732&partnerID=40>

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Pediatricians and primary care physicians may be uncomfortable diagnosing Chronic Fatigue Syndrome in children because a good diagnostic tool has not been available. Deferring a diagnosis, however, may lead to apprehension, over-utilization of medical resources in a search for validity, a delay in treatment, and possibly inappropriate coping techniques. This case-based article discusses symptoms and signs seen in adolescent patients with CFS, evaluation of suspect cases, and both current and future diagnostic case definitions. © 2006 by The Haworth Press, Inc. All rights reserved.

Vernon S.D., Reeves W.C.

Evaluation of autoantibodies to common and neuronal cell antigens in Chronic Fatigue Syndrome

2005 Journal of Autoimmune Diseases 2

<http://www.scopus.com/inward/record.url?eid=2-s2.0-23044500863&partnerID=40>

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People with chronic fatigue syndrome (CFS) suffer from multiple symptoms including fatigue, impaired memory and concentration, unrefreshing sleep and musculoskeletal pain. The exact causes of CFS are not known, but the symptom complex resembles that of several diseases that affect the immune system and autoantibodies may provide clues to the various etiologies of CFS. We used ELISA, immunoblot and commercially available assays to test serum from subjects enrolled in a physician-based surveillance study conducted in Atlanta, Georgia and a population-based study in Wichita, Kansas for a number of common autoantibodies and antibodies to neuron specific antigens. Subsets of those with CFS had higher rates of antibodies to microtubule-associated protein 2 (MAP2) ($p = 0.03$) and ssDNA ($p = 0.04$). There was no evidence of higher rates for several common nuclear and cellular antigens in people with CFS. Autoantibodies to specific host cell antigens may be a useful approach for identifying subsets of people with CFS, identify biomarkers, and provide clues to CFS etiologies. © 2005 Vernon and Reeves; licensee BioMed Central Ltd.

Garralda M.E., Rangel L.

Chronic fatigue syndrome of childhood: Comparative study with emotional disorders

2005 European Child and Adolescent Psychiatry 14 (8); 424 – 430

<http://www.scopus.com/inward/record.url?eid=2-s2.0-28844470356&partnerID=40>

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Objective: To examine clinical specificity in chronic fatigue syndrome (CFS) of childhood, by comparing clinical features in childhood CFS and in emotional disorders (ED). Method Sample: 28 children with CFS; 27 with ED. Measures: History of disorder; K-SADS psychiatric interviews; self-esteem and physical symptoms questionnaires; pre-morbid history, behavioural and personality assessments. Results: There were high levels of comorbid emotional disorders in children with CFS, and the two groups were comparable on self-esteem, but CFS children endorsed more fatigue and other somatic symptoms. The two groups were comparable on age at illness onset, but parents of children with CFS reported more biological illness precipitants, more pre-morbid recurrent medical problems and infections. The CFS group had fewer pre-morbid psychological problems and less psychiatric comorbidity than the ED group. Conclusion: There is considerable clinical overlap between CFS and ED of childhood, but there are also differences in clinical presentation between these disorders. © Steinkopff Verlag 2005.

Casado B., Zanone C., Annovazzi L., Iadarola P., Whalen G., Baraniuk J.N.

Urinary electrophoretic profiles from chronic fatigue syndrome and chronic fatigue syndrome/fibromyalgia patients: A pilot study for achieving their normalization

2005 Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences 814 (1); 43 – 51

<http://www.scopus.com/inward/record.url?eid=2-s2.0-10944242220&partnerID=40>

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Aim of our study was to determine if there were distinct, disease-related patterns of urinary analytes in chronic fatigue syndrome (CFS) and chronic fatigue syndrome/fibromyalgia (CFS/FM) compared to

normal controls (NC). Urine was collected from these subjects for two consecutive 24 h periods and aliquots were submitted to micellar electrokinetic chromatography (MEKC). To compensate for the differences in peak migration times, these were normalized from the 35 min duration of run to a 100-point scale, and each peak was assigned its normalized time measure. Peak heights were also normalized by dividing the mAU by that of the internal standard (creatinine) and multiplying by 100. MEKC with normalization for peak height and migration time generated comparable results within each of the patient groups. CFS/FM and CFS had significant differences in peaks compared to NC that may be of significance as biomarkers of illnesses. © 2004 Elsevier B.V. All rights reserved.

Sullivan P.F., Evengard B., Jacks A., Pedersen N.L.
Twin analyses of chronic fatigue in a Swedish national sample

2005 Psychological Medicine 35 (9); 1327 – 1336

<http://www.scopus.com/inward/record.url?eid=2-s2.0-24644491820&partnerID=40>

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Background. Chronic fatigue has infrequently been studied in twins. Data from twin studies can inform clinical and research approaches to the management and etiology of human complex traits. Method. The authors obtained telephone interview data on current chronic fatigue from 31 406 individuals twins in the Swedish Twin Registry (aged 42-64 years, 75.68% response rate), from both members of 12 407 pairs and from one member of 6592 pairs. Of the complete pairs, 3269 pairs were monozygotic, 9010 pairs dizygotic, and 128 pairs of unknown zygosity. Structural equation twin modeling was used to estimate the latent genetic architecture of varying definitions of fatiguing illness. Results. Estimates of additive genetic effects, shared environmental effects, and individual-specific environmental effects were similar in males and females. No definition of current fatiguing illness (ranging from any fatigue to CFS-like illness) was strikingly distinctive. Individual-specific effects were the predominant source of variation, followed by modest genetic influences. We could not exclude a small but conceptually important contribution of shared environmental effects. Conclusions. Current fatiguing illness appears to be a complex trait resulting from both environmental and genetic sources of variation without pronounced differences by gender. © 2005 Cambridge University Press.

Furberg H., Olarte M., Afari N., Goldberg J., Buchwald D., Sullivan P.F.
The prevalence of self-reported chronic fatigue in a U.S. twin registry

2005 Journal of Psychosomatic Research 59 (5); 283 – 290

<http://www.scopus.com/inward/record.url?eid=2-s2.0-27444432958&partnerID=40>

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Objective: To investigate the prevalence and correlates of various definitions of self-reported lifetime fatiguing illness in a U.S. twin registry. Methods: Data from 4591 female and male twins from the population-based Mid-Atlantic Twin Registry were available for this study. Variables representing different definitions of lifetime fatiguing illness and personal characteristics were obtained through questionnaires. Odds ratios and 95% confidence intervals were calculated as measures of association between fatigue and gender. Kaplan-Meier curves were produced to examine the age at onset for lifetime fatiguing illnesses. Results: Prevalences for different definitions of self-reported lifetime fatigue ranged from 36.7% for any fatigue to 2.7% for chronic fatigue syndrome-like illness. Females were two to three times more likely to report fatigue than males. Gender differences increased as fatigue

definitions grew more restrictive. Ages at onset of chronic fatiguing illness were significantly earlier and the number of ancillary symptoms was greater for females than males. People with lifetime fatigue had significantly more compromised functional status than people without lifetime fatigue. Conclusion: The prevalence of self-reported lifetime fatiguing illness varied widely depending upon how it was defined. Given the debilitating consequences of fatiguing illnesses, the reasons for the female predominance and the earlier onset in women should receive increased research priority. © 2005 Elsevier Inc. All rights reserved.

Evengard B., Jacks A., Pedersen N.L., Sullivan P.F.
The epidemiology of chronic fatigue in the Swedish Twin Registry

2005 Psychological Medicine 35 (9); 1317 – 1326

<http://www.scopus.com/inward/record.url?eid=2-s2.0-24644506227&partnerID=40>

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Background. Chronic fatigue syndrome (CFS) remains an idiopathic and controversial entity. Method. We screened 31405 individual members of the Swedish Twin Registry (aged 42-64 years) for the symptoms of fatiguing illness via a telephone questionnaire. We refined self-reported symptoms via data from several national registries and from physician review of all available medical records in order to approximate closely the dominant case definition of CFS. Findings. The 6-month prevalence of CFS-like illness was 2.36% (95% CI 2.19-2.53) and was markedly higher in women than men, odds ratio 3.92 (95% CI 3.24-4.72) with no significant association with age or years of education. There was a highly significant association with occupation that disappeared after accounting for gender. Interpretation. CFS-like illness may be more common than previously acknowledged. There is a marked increase in risk by gender. Previous reports that CFS is more prevalent in individuals in certain occupational categories were not confirmed and may have been due to confounding by gender. © 2005 Cambridge University Press.

Cheol H.K., Ho C.S., Chang W.W.
Prevalence of chronic fatigue and chronic fatigue syndrome in Korea: Community-based primary care study

2005 Journal of Korean Medical Science 20 (4); 529 – 534

<http://www.scopus.com/inward/record.url?eid=2-s2.0-24644450358&partnerID=40>

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There have been many epidemiological and clinical researches on chronic fatigue (CF) and chronic fatigue syndrome (CFS) since the 1990s, but such studies have been quite limited in Korea. The aim of this study was to investigate the point prevalence of CF and CFS in patients who visited community-based eight primary care clinics in Korea. The study subjects were 1,648 patients aged 18 yr and over who visited one of eight primary care clinics in Korea between the 7th and 17th of May 2001. The physicians determined the status of the subjects through fatigue-related questionnaires, medical history, physical examination, and laboratory tests. The subjects were categorized into no fatigue, prolonged fatigue, CF and then CF were further classified to medically explained CF (Physical CF and Psychological CF) and medically unexplained CF (CFS and idiopathic chronic fatigue). The point prevalence of CF and CFS were 8.4% (95% CI 7.1-9.7%) and 0.6% (95% CI 0.2-1.0%). Medically explained CF was 80.5% of CF, of which 57.1% had psychological causes. The clinical characteristics of

CFS were distinguished from explained CF. CF was common but CFS was rare in community-based primary care settings in Korea. Copyright © The Korean Academy of Medical Sciences.

Wernham W., Pheby D., Saffron L.

Risk factors for the development of severe ME/CFS - A pilot study

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-22844451966&partnerID=40>

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The pilot phase is reported of a case-control study to determine risk factors for severe CFS/ME. One hundred fifty-seven members of the ME Association, selected at random, were sent postal questionnaires, with a 56% response. The Barthel index was used as a validated proxy measure to distinguish severe disease (cases) and those less severe. Thirteen of 88 respondents had severe disease, and 44 mild disease. Two matched controls from the 'mild' group were selected per case. Of possible risk factors, odds ratios greater than 2 were found for comorbidities, damaging initial treatment and occupational chemical exposure, although in this study they were not statistically significant. These data suggest that additional studies are warranted. © 2004 by The Haworth Press, Inc. All rights reserved.

Viner R., Hotopf M.

Childhood predictors of self reported chronic fatigue syndrome/myalgic encephalomyelitis in adults: National birth cohort study

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-7044238934&partnerID=40>

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Objective: To study childhood risk factors for chronic fatigue syndrome in adult life. Design: Examination of data from the 1970 British birth cohort. Participants: 16 567 babies born 5-11 April 1970, followed up at 5, 10, 16, and 29-30 years. Main outcome measures: Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). identified by self report at age 30 years. Data from childhood from questionnaires given to parents and teachers. Maternal mental health assessed with the malaise inventory. Results: 93 (0.8%, 95% confidence interval 0.7 to 1.0) of 11 261 participants reported ever having CFS/ME, and 48 (0.4%, 0.3 to 0.6) had the condition currently. Higher risk of CFS/ME was associated with having a limiting longstanding condition in childhood (odds ratio 2.3, 1.4 to 3.9), female sex (2.3, 1.4 to 2.6), and high social class in childhood (2.2, 1.4 to 3.5). Higher levels of exercise in childhood were associated with lower risk (0.5, 0.2 to 0.9). Maternal psychological disorder, psychological problems in childhood, birth weight, birth order, atopy, obesity, school absence, academic ability, and parental illness were not associated with risk of CFS/ME. Conclusions: We identified no association between maternal or child psychological distress, academic ability, parental illness, atopy, or birth order and increasing risk of lifetime CFS/ME. Sedentary behaviour increased the risk.

Tseng C.-L., Natelson B.H.

Few gender differences exist between women and men with chronic fatigue syndrome

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Chronic fatigue syndrome (CFS) is generally considered to be a women's health issue, but the illness occurs also in men. The research objective of this study was to determine if illness patterns and functional status differed between the sexes. Because our own data showed that women with CFS have significantly more comorbid fibromyalgia or multiple chemical sensitivity than men, we eliminated patients with these comorbid conditions from our evaluation. Women with CFS were quite similar to men with CFS in terms of demographics, psychiatric status, functional status, and assessments of disability. Women reported more infectious/flu-like symptoms (represented by a factor derived from factor analysis) than men, but these differences were insignificant after controlling for other variables. Cluster analysis revealed that women were more likely than men to fall in the cluster characterized by symptom severity. Differences found were those of degree rather than of type; strikingly different illness patterns-suggestive of different pathophysiological processes between the sexes-were not found. © 2004 Plenum Publishing Corporation.

Huibers M.J.H., Kant I.J., Swaen G.M.H., Kasl S.V.

Prevalence of chronic fatigue syndrome-like caseness in the working population: Results from the Maastricht cohort study

2004 Occupational and Environmental Medicine 61 (5); 464 – 466

<http://www.scopus.com/inward/record.url?eid=2-s2.0-2442563574&partnerID=40>

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Aim: To determine the prevalence of chronic fatigue syndrome (CFS)-like caseness in the working population. Methods: Using data from the prospective Maastricht Cohort Study on Fatigue at Work, the prevalence and incidence of CFS-like cases (employees meeting research criteria for CFS) were determined among 5499 employees who responded to the follow up assessment 3 years and 8 months after baseline. Results: Of the 5499 employees, 199 (3.6%) were identified as CFS-like cases. By deleting possible CFS-like cases at baseline, the annual incidence of CFS-like caseness was estimated to be 85 per 10 000. Twenty employees (0.36%) reported having been diagnosed with CFS by a physician. Conclusions: The prevalence of CFS-like cases (3.6%) was considerably higher than the prevalence of CFS reported in previous studies (0.006-3%). These findings suggest that the CFS-like caseness may be underdetected in the working population and perhaps in other populations as well.

Bierl C., Nisenbaum R., Haoglin D.C., Randall B., Jones A.-B., Unger E.R., Reeves W.C.

Regional distribution of fatiguing illnesses in the United States: A pilot study

2004 Population Health Metrics 2

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4344652787&partnerID=40>

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Background. Chronic fatigue syndrome (CFS) is a debilitating illness with no known cause or effective therapy. Population-based epidemiologic data on CFS prevalence are critical to put CFS in a realistic context for public health officials and others responsible for allocating resources. Methods. We conducted a pilot random-digit-dialing survey to estimate the prevalence of fatiguing illnesses in different geographic regions and in urban and rural populations of the United States. This report

focuses on 884 of 7,317 respondents 18 to 69 years old. Fatigued (440) and randomly selected non-fatigued (444) respondents completed telephone questionnaires concerning fatigue, other symptoms, and medical history. Results. We estimated 12,186 per 100,000 persons 18 to 69 years of age suffered from fatigue lasting for at least 6 months (chronic fatigue), and 1,197 per 100,000 described an illness that, though lacking clinical evaluation, met criteria for CFS (CFS-like). Chronic fatigue and CFS-like illness were more common in rural than in urban populations, although the differences were not significant. The prevalence of these fatiguing illnesses did not differ meaningfully among the four regions surveyed, and no significant geographic trends were observed. Conclusions. This investigation estimated that nearly 2.2 million American adults suffer from CFS-like illness. The study also suggested the need to focus future investigations of fatigue on populations with lower incomes and less education. There was no evidence for regional differences in the occurrence of fatiguing illnesses. © 2004 Bierl et al; licensee BioMed Central Ltd.

Fatigue

Weinstein A.A., Drinkard B.M., Diao G., Furst G., Dale J.K., Straus S.E., Gerber L.H.
Exploratory Analysis of the Relationships between Aerobic Capacity and Self-Reported Fatigue in Patients with Rheumatoid Arthritis, Polymyositis, and Chronic Fatigue Syndrome

2009 PM and R 1 (7); 620 - 628

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67649541075&partnerID=40>

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Objective: To determine if self-reported levels of physical activity and fatigue are related to peak oxygen uptake (VO₂peak) and whether these relationships differ among the patient groups (rheumatoid arthritis [RA], polymyositis [PM], and chronic fatigue syndrome [CFS]). Design: Correlational investigation. Setting: Two ambulatory research clinics at the National Institutes of Health, Clinical Center, Bethesda, MD. Participants: There were 9 patients with PM, 10 with RA, and 10 with CFS. All patients met case criteria for their respective diagnoses. Methods/Main Outcome Measurements: VO₂peak during bicycle ergometry and self-reported fatigability, fatigue, and physical activity. VO₂peak was used as the criterion measurement of physiological fatigue with which the self-reported variables were compared. Results: The Pearson r revealed that self-reported physical activity correlated with VO₂peak ($r = .61$, $P = .01$). However, fatigability and fatigue did not correlate with VO₂peak. Linear regression analysis was performed to assess the effects of diagnosis group, self-reported activity level or fatigue, and their interaction. A trend in the data showed a distinctive relationship between fatigue/fatigability within the 3 groups. In addition, when controlling for group status, self-reported activity predicted aerobic capacity as measured by VO₂peak. Conclusions: This study confirms that patients with chronic, but stable RA, PM, or CFS are fatigued and have significantly decreased aerobic capacity. Self-reports of physical activity predicted VO₂peak, and may be used as an indicator of activity-based aerobic capacity. Self-reports of fatigue, however, did not correlate with VO₂peak and hence are assessing something other than an index of aerobic capacity, and provide additional information about patients' perceptions, which will require further investigation. © 2009 American Academy of Physical Medicine and Rehabilitation.

Pietrangelo T., Toniolo L., Paoli A., Fulle S., Puglielli C., Fano G., Reggiani C.
Functional characterization of muscle fibres from patients with chronic fatigue syndrome: Case-control study

2009 International Journal of Immunopathology and Pharmacology 22 (2); 427 – 436

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650480371&partnerID=40>

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Chronic fatigue syndrome (CFS) is a disabling condition characterized by unexplained chronic fatigue that impairs normal activities. Although immunological and psychological aspects are present,

symptoms related to skeletal muscles, such as muscle soreness, fatigability and increased lactate accumulation, are prominent in CFS patients. In this case-control study, the phenotype of the same biopsy samples was analyzed by determining i) fibre-type proportion using myosin isoforms as fibre type molecular marker and gel electrophoresis as a tool to separate and quantify myosin isoforms, and ii) contractile properties of manually dissected, chemically made permeable and calcium-activated single muscle fibres. The results showed that fibre-type proportion was significantly altered in CSF samples, which showed a shift from the slow- to the fast-twitch phenotype. Cross sectional area, force, maximum shortening velocity and calcium sensitivity were not significantly changed in single muscle fibres from CSF samples. Thus, the contractile properties of muscle fibres were preserved but their proportion was changed, with an increase in the more fatigue-prone, energetically expensive fast fibre type. Taken together, these results support the view that muscle tissue is directly involved in the pathogenesis of CSF and it might contribute to the early onset of fatigue typical of the skeletal muscles of CFS patients. Copyright © by Biolife, s.a.s.

Jammes Y., Steinberg J.G., Delliaux S., Bregeon F.

Chronic fatigue syndrome combines increased exercise-induced oxidative stress and reduced cytokine and Hsp responses

2009 Journal of Internal Medicine 266 (2); 196 – 206

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650485309&partnerID=40>

UMR MD2 (P2COE), Université de la Méditerranée and Pulmonary Function Laboratory, North Hospital, Hôpitaux de Marseille, France; UMR MD2 P2COE, Faculté de Médecine, Boulevard Pierre Dramard, 13916 Marseille cedex 20, France Jammes Y, Steinberg JG, Delliaux S, Bregeon F (Université de la Méditerranée and Pulmonary Function Laboratory, North Hospital, Assistance Publique - Hôpitaux de Marseille, France).

Chronic fatigue syndrome combines increased exercise-induced oxidative stress and reduced cytokine and Hsp responses. *J Intern Med* 2009; *J Intern Med* 2009; 266: 196-206. Objectives. As heat shock proteins (Hsp) protect the cells against the deleterious effects of oxidative stress, we hypothesized that Hsp expression might be reduced in patients suffering from chronic fatigue syndrome (CFS) who present an accentuated exercise-induced oxidative stress. Design. This case-control study compared nine CFS patients to a gender-, age- and weight-matched control group of nine healthy sedentary subjects. Interventions. All subjects performed an incremental cycling exercise continued until exhaustion. We measured ventilation and respiratory gas exchange and evoked compound muscle potential (M-wave) recorded from vastus lateralis. Repetitive venous blood sampling allowed measurements of two markers of oxidative stress [thiobarbituric acid reactive substances (TBARS) and reduced ascorbic acid (RAA)], two cytokines (IL-6 and TNF- $\hat{\pm}$) and two Hsp (Hsp27 and Hsp70) at rest, during maximal exercise and the 60-min recovery period. Results. Compared with controls, resting CFS patients had low baseline levels of RAA and Hsp70. Their response to maximal exercise associated (i) M-wave alterations indicating reduced muscle membrane excitability, (ii) early and accentuated TBARS increase accompanying reduced changes in RAA level, (iii) absence of significant increase in IL-6 and TNF- $\hat{\pm}$, and (iv) delayed and marked reduction of Hsp27 and Hsp70 variations. The post-exercise increase in TBARS was accentuated in individuals having the lowest variations of Hsp27 and Hsp70. Conclusions. The response of CFS patients to incremental exercise associates a lengthened and accentuated oxidative stress, which might result from delayed and insufficient Hsp production. © 2009 Blackwell Publishing Ltd.

Burton C., Knoop H., Popovic N., Sharpe M., Bleijenberg G.
Reduced complexity of activity patterns in patients with Chronic Fatigue Syndrome: A case control study

2009 BioPsychoSocial Medicine 3

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67649292740&partnerID=40>

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Background: Chronic fatigue syndrome (CFS) is an illness characterised by pervasive physical and mental fatigue without specific identified pathological changes. Many patients with CFS show reduced physical activity which, though quantifiable, has yielded little information to date. Nonlinear dynamic analysis of physiological data can be used to measure complexity in terms of dissimilarity within timescales and similarity across timescales. A reduction in these objective measures has been associated with disease and ageing. We aimed to test the hypothesis that activity patterns of patients with CFS would show reduced complexity compared to healthy controls. Methods: We analysed continuous activity data over 12 days from 42 patients with CFS and 21 matched healthy controls. We estimated complexity in two ways, measuring dissimilarity within timescales by calculating entropy after a symbolic dynamic transformation of the data and similarity across timescales by calculating the fractal dimension using allometric aggregation. Results: CFS cases showed reduced complexity compared to controls, as evidenced by reduced dissimilarity within timescales (mean (SD) Renyi(3) entropy 4.05 (0.21) vs. 4.30 (0.09), $t = -6.6$, $p < 0.001$) and reduced similarity across timescales (fractal dimension 1.19 (0.04) vs. 1.14 (0.04), $t = 4.2$, $p < 0.001$). This reduction in complexity persisted after adjustment for total activity. Conclusion: Patients with CFS show evidence of reduced complexity of activity patterns. Measures of complexity applied to activity have potential value as objective indicators for CFS. © 2009 Burton et al; licensee BioMed Central Ltd.

VanNess J.M., Snell C.R., Stevens S.R.
Diminished cardiopulmonary capacity during post-exertional malaise

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-39049168973&partnerID=40>

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Reduced functional capacity and post-exertional malaise following physical activity are hallmark symptoms of Chronic Fatigue Syndrome (CFS). That these symptoms are often delayed may explain the equivocal results for clinical cardiopulmonary exercise testing with CFS patients. The reproducibility of VO₂max in healthy subjects is well documented. This may not be the case with CFS due to delayed recovery symptoms. Purpose: To compare results from repeated exercise tests as indicators of post-exertional malaise in CFS. Methods: Peak oxygen consumption (VO₂ peak), percentage of predicted peak heart rate (HR%), and VO₂ at anaerobic threshold (AT), were compared between six CFS patients and six control subjects for two maximal exercise tests separated by 24 hours. Results: Multivariate analysis showed no significant differences between control and CFS, respectively, for test 1: VO₂ peak (28.4 \bar{A} ± 7.2 ml/kg/min; 26.2 \bar{A} ± 4.9 ml/kg/min), AT (17.5 \bar{A} ± 4.8 ml/kg/min; 15.0 \bar{A} ± 4.9 ml/kg/min) or HR% (87.0 \bar{A} ± 25.4%; 94.8 \bar{A} ± 8.8%). However, for test 2 the CFS patients achieved significantly lower values for both VO₂peak (28.9 \bar{A} ± 8.0 ml/kg/min; 20.5 \bar{A} ± 1.8 ml/kg/min, $p = 0.031$) and AT (18.0 \bar{A} ± 5.2 ml/kg/min; 11.0 \bar{A} ± 3.4 ml/kg/min, $p = 0.021$). HR% was not significantly different (97.6 \bar{A} ± 27.2%; 87.8 \bar{A} ± 9.3%, $p = 0.07$). A follow-up classification analysis differentiated between CFS patients and controls with an overall accuracy of 92%. Conclusion: In the absence of a second exercise test, the lack of any significant differences for

the first test would appear to suggest no functional impairment in CFS patients. However, the results from the second test indicate the presence of a CFS related post-exertional malaise. It might be concluded then that a single exercise test is insufficient to demonstrate functional impairment in CFS patients. A second test may be necessary to document the atypical recovery response and protracted malaise unique to CFS. Copyright © by The Haworth Press, Inc. All rights reserved.

Neary J.P., Roberts A.D.W., Leavins N., Harrison M.F., Croll J.C., Sexsmith J.R. Prefrontal cortex oxygenation during incremental exercise in chronic fatigue syndrome 2008 *Clinical Physiology and Functional Imaging* 28 6 364 372 <http://www.scopus.com/inward/record.url?eid=2-s2.0-54249127818&partnerID=40> Faculty of Kinesiology and Health Studies, University of Regina, Regina, SK S4S 0A2, Canada; Faculty of Kinesiology, University of New Brunswick, Fredericton, NB, Canada This study examined the effects of maximal incremental exercise on cerebral oxygenation in chronic fatigue syndrome (CFS) subjects. Furthermore, we tested the hypothesis that CFS subjects have a reduced oxygen delivery to the brain during exercise. Six female CFS and eight control (CON) subjects (similar in height, weight, body mass index and physical activity level) performed an incremental cycle ergometer test to exhaustion, while changes in cerebral oxygenation (HbO₂), deoxy-haemoglobin (HHb), total blood volume (tHb=HbO₂+HHb) and O₂ saturation [tissue oxygenation index (TOI), %] was monitored in the left prefrontal lobe using a near-infrared spectrophotometer. Heart rate (HR) and rating of perceived exertion (RPE) were recorded at each workload throughout the test. Predicted VO_{2peak} in CFS (1331±377 ml) subjects was significantly (P < 0.05) lower than the CON group (1990±332 ml), and CFS subjects achieved volitional exhaustion significantly faster (CFS: 351±224 s; CON: 715±176 s) at a lower power output (CFS: 100±39 W; CON: 163±34 W). CFS subjects also exhibited a significantly lower maximum HR (CFS: 154±13 bpm; CON: 186±11 bpm) and consistently reported a higher RPE at the same absolute workload when compared with CON subjects. Prefrontal cortex HbO₂, HHb and tHb were significantly lower at maximal exercise in CFS versus CON, as was TOI during exercise and recovery. The CFS subjects exhibited significant exercise intolerance and reduced prefrontal oxygenation and tHb response when compared with CON subjects. These data suggest that the altered cerebral oxygenation and blood volume may contribute to the reduced exercise load in CFS, and supports the contention that CFS, in part, is mediated centrally. © 2008 The Authors Journal compilation © 2008 Scandinavian Society of Clinical Physiology and Nuclear Medicine.

Harvey S.B., Wadsworth M., Wessely S., Hotopf M.
Etiology of chronic fatigue syndrome: testing popular hypotheses using a national birth cohort study.

2008 *Psychosomatic medicine* 70 (4); 488 - 495

<http://www.scopus.com/inward/record.url?eid=2-s2.0-45149109390&partnerID=40>

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OBJECTIVE: To review the etiology of chronic fatigue syndrome (CFS) and test hypotheses relating to immune system dysfunction, physical deconditioning, exercise avoidance, and childhood illness experiences, using a large prospective birth cohort. **METHODS:** A total of 4779 participants from the Medical Research Council's National Survey of Health and Development were prospectively followed for the first 53 years of their life with >20 separate data collections. Information was collected on childhood and parental health, atopic illness, levels of physical activity, fatigue, and participant's weight and height at multiple time points. CFS was identified through self-report during a semistructured interview at age 53 years with additional case notes review. **RESULTS:** Of 2983 participants assessed at age 53 years, 34 (1.1%, 95% Confidence Interval 0.8-1.5) reported a diagnosis of CFS. Those who reported CFS were no more likely to have suffered from childhood illness or atopy. Increased levels of exercise throughout childhood and early adult life and a lower body mass index were associated with an increased risk of later CFS. Participants who later reported CFS continued to exercise more frequently even after they began to experience early symptoms of fatigue. **CONCLUSIONS:** Individuals who exercise frequently are more likely to report a diagnosis of CFS in later life. This may be due to the direct effects of this behavior or associated personality factors. Continuing to be active despite increasing fatigue may be a crucial step in the development of CFS.

Yoshiuchi K., Cook D.B., Ohashi K., Kumano H., Kuboki T., Yamamoto Y., Natelson B.H.
A real-time assessment of the effect of exercise in chronic fatigue syndrome

2007 Physiology and Behavior 92 (5); 963 – 968

<http://www.scopus.com/inward/record.url?eid=2-s2.0-36048971662&partnerID=40>

Department of Neurosciences, University of Medicine and Dentistry, New Jersey - New Jersey Medical School, United States; Department of Psychosomatic Medicine, Faculty of Medicine, the University of Tokyo, Japan; Research Service, William S. Middleton Memorial Veterans Hospital, the Department of Kinesiology, Madison, United States; Educational Physiology Laboratory, Graduate School of Education, the University of Tokyo, Japan

Patients with chronic fatigue syndrome (CFS) report substantial symptom worsening after exercise. However, the time course over which this develops has not been explored. Therefore, the objective of this study was to investigate the influence of exercise on subjective symptoms and on cognitive function in CFS patients in natural settings using a computerized ecological momentary assessment method, which allowed us to track the effects of exercise within and across days. Subjects were 9 female patients with CFS and 9 healthy women. A watch-type computer was used to collect real-time data on physical and psychological symptoms and cognitive function for 1 week before and 2 weeks after a maximal exercise test. For each variable, we investigated temporal changes after exercise using multilevel modeling. Following exercise, physical symptoms did get worse but not until a five-day delay in CFS patients. Despite this, there was no difference in the temporal pattern of changes in psychological symptoms or in cognitive function after exercise between CFS patients and controls. In conclusion, physical symptoms worsened after several days delay in patients with CFS following exercise while psychological symptoms or cognitive function did not change after exercise. © 2007 Elsevier Inc. All rights reserved.

Yokoyama T., Lisi T.L., Moore S.A., Sluka K.A.

Muscle Fatigue Increases the Probability of Developing Hyperalgesia in Mice

2007 Journal of Pain 8 (9); 692 - 699

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34548455349&partnerID=40>

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Chronic muscle pain is a major clinical problem that is often associated with fatigue. Conversely, chronic fatigue conditions are commonly associated with muscle pain. We tested the hypothesis that muscle fatigue enhances hyperalgesia associated with injection of acidic saline into muscle. We evaluated mechanical sensitivity of the paw (von Frey) in mice after 2 intramuscular injections of saline (20 μ L; pH 4, pH 5, pH 6, pH 7.2) in a fatigue and a control group. To induce fatigue, mice were run for 2 h/day for 2 days prior to the first injection and 2 h/day for 2 days prior to the second injection. Muscle lactate, pCO₂, pO₂, creatinine kinase, phosphate, and histology were examined after the fatigue task and compared to a control group. Grip force was significantly decreased after 2 h of running indicating fatigue. The fatigue task did not induce muscle damage as there was no difference in muscle lactate, pCO₂, pO₂, creatinine kinase, phosphate, or histology. The fatigue task altered the dose-response relationship to intramuscular acidic saline injections. Mechanical hyperalgesia was observed in both fatigue and control groups after intramuscular injection of pH 4.0, but only the fatigue group after injection of pH 5.0. Neither the fatigue nor the control group developed hyperalgesia in response to intramuscular injection of pH 6.0 or pH 7.2. In conclusion, fatigue modified the susceptibility of mice to acid injection of pH 5.0 to result in mechanical hyperalgesia after 2 injections of pH 5.0. The fatigue task did not produce measurable changes in the muscle tissue suggesting a central mechanism mediating the enhancement of hyperalgesia. Perspective: These data therefore show that muscle fatigue can enhance the likelihood that one develops pain to a mild insult. Clinically, this could relate to the development of pain from such conditions as repetitive strain injury, and may relate to the interrelationship between chronic pain and fatigue. © 2007 American Pain Society.

Wallman K.E., Sacco P.

Sense of effort during a fatiguing exercise protocol in chronic fatigue syndrome

2007 Research in Sports Medicine 15 (1); 47 – 59

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847665546&partnerID=40>

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The purpose of this study was to determine whether chronic fatigue syndrome (CFS) subjects would produce greater force production in their matching limb during a fatiguing contralateral limb-matching task of the elbow flexors, compared with healthy, matched controls. Eight CFS subjects and 8 healthy, matched control subjects participated in a fatiguing task that consisted of intermittent submaximal contractions (30% maximal voluntary contraction) of the nondominant arm performed over a 45 min duration. Each minute, the subject attempted to match the force of the nondominant arm with their dominant arm (without visual feedback for the dominant arm). Results showed that average matching force and ratings of perceived effort values were significantly higher in the CFS group during the fatiguing task ($P = 0.04$, $P = 0.02$, respectively). This study demonstrated objectively that CFS subjects experienced a greater sense of effort in the elbow flexors while performing a fatiguing task. Copyright © Taylor & Francis Group, LLC.

Van Houdenhove B., Verheyen L., Pardaens K., Luyten P., Van Wambeke P.

Rehabilitation of decreased motor performance in patients with chronic fatigue syndrome: Should we treat low effort capacity or reduced effort tolerance?

2007 Clinical Rehabilitation 21 (12); 1121 – 1142

<http://www.scopus.com/inward/record.url?eid=2-s2.0-38349082373&partnerID=40>

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Aim: The aetiology, pathophysiology, diagnostic delineation and treatment of chronic fatigue syndrome (CFS) remain a matter of debate. Here some aspects of the debate are elucidated, with a particular focus on the patients' decreased motor performance. **Hypothesis:** The pathophysiological basis of decreased motor performance in CFS may, theoretically, involve three components: (1) a peripheral energetic deficit (impaired oxidative metabolism and/or physical deconditioning); (2) a central perceptual disturbance (higher effort sense or increased 'interoception'); and (3) a fundamental failure of the neurobiological stress system, leading to an abnormal 'sickness response'. It is proposed that the first two components may lead to low effort capacity, while the third component may lead to reduced effort tolerance. Although there is evidence for low effort capacity influencing symptoms and functional limitations in CFS, it is assumed that reduced effort tolerance might be the primary disturbance in CFS. **Diagnostic implications:** Distinguishing low effort capacity and reduced effort tolerance may contribute to a refinement of current diagnostic criteria of CFS and the identification of subgroups. **Therapeutic implications:** The above-mentioned distinction may make it possible to formulate a rationale for an effective implementation and adequate outcome evaluation of rehabilitation strategies in CFS. **Research implications:** This new heuristic framework may inform future research aimed at disentangling the complex determination of impaired motor performance in CFS, as well as studies aimed at customizing treatment to different subtypes of patients. © SAGE Publications 2007 Los Angeles, London, New Delhi and Singapore.

Takken T., Henneken T., Van De Putte E., Helders P., Engelbert R.
Exercise testing in children and adolescents with chronic fatigue syndrome

2007 International Journal of Sports Medicine 28 (7); 580 – 585

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34447511573&partnerID=40>

Pediatric Physical Therapy and Exercise Physiology, UMC Utrecht, Utrecht, Netherlands; Department of Pediatrics, UMC Utrecht, Utrecht, Netherlands; UMC Utrecht, Pediatric Physical Therapy and Exercise Physiology, PO Box 85090, 3508 AB Utrecht, Netherlands

The objective of this study was to evaluate exercise capacity in children and adolescents diagnosed with Chronic Fatigue Syndrome (CFS). We examined 20 patients (12 girls and 8 boys; mean age 14.9 ± 3.7 years) diagnosed with CFS. Exercise capacity was measured using a maximal exercise test on a bicycle ergometer and an expired gas analysis system. Fatigue was assessed using a questionnaire and a daily activity diary was used to describe activities for three days. Z-scores were calculated using age- and sex-matched reference values. Z-scores in children and adolescents with CFS were -0.33 ± 1.0 ($p = 0.17$) for peak oxygen uptake, -1.13 ± 1.41 ($p = 0.002$) for relative peak oxygen uptake [ml/kg/min] and -0.93 ± 1.29 ($p = 0.07$) for maximal work load. Both heart rate and blood pressure at peak performance were significantly reduced compared to reference values. Fatigue levels were significantly positively associated with age and negatively with blood pressure at peak exercise ($p < 0.05$). In conclusion maximum exercise testing was feasible in young people with CFS. Maximal exercise capacity was only reduced in a minority of the patients and was related to current physical activity levels. © Georg Thieme Verlag KG Stuttgart.

Nijs J., Zwinnen K., Meeusen R., De Geus B., De Meirleir K.
Comparison of two exercise testing protocols in patients with chronic fatigue syndrome

2007 Journal of Rehabilitation Research and Development 44 (4); 553 – 559

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34548055668&partnerID=40>

Department of Human Physiology, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Brussels, Belgium; Division of Musculoskeletal Physiotherapy, Department of Health Care Sciences, University College Antwerp, Antwerp, Belgium; Vrije Universiteit Brussel, Mfys/Sport, KRO-gebouw -1, Laarbeeklaan 101, B-1090 Brussels, Belgium

This study examined whether a linear exercise stress-testing protocol generated different peak exercise performance variables than a stepwise exercise testing protocol in patients with chronic fatigue syndrome (CFS). We conducted a comparative study with patients randomly allocated to one of two exercise testing protocols. Twenty-eight women with CFS completed two self-reported measures (the CFS Symptom List and the CFS Activities and Participation Questionnaire) and then performed until exhaustion either the linear or the stepwise exercise testing protocol with continuous monitoring of physiological variables (heart rate and oxygen uptake). At baseline, we found no significant differences in demographic features and health status between groups ($p > 0.05$). Based on ratio peak workload/peak oxygen uptake, mechanical efficiency was lower among the subjects performing the stepwise protocol ($p = 0.002$). When we analyzed the mean linear regression slope values between oxygen uptake and workload from each subject's minute-by-minute exercise data points, we found that mechanical efficiency was lower among the subjects performing the stepwise protocol ($p = 0.039$). Apart from mechanical efficiency, we found no differences in exercise performance data between groups ($p > 0.05$). Our results suggest that the difference between linear and stepwise exercise protocols cannot account for all discrepancies of previous studies on exercise performance data in women with CFS, but they do suggest that the nature of the exercise testing protocol influences mechanical efficiency in these patients. Further study is warranted.

Nijs J., Demol S., Wallman K.

Can Submaximal Exercise Variables Predict Peak Exercise Performance in Women with Chronic Fatigue Syndrome?

2007 Archives of Medical Research 38 (3); 350 – 353

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847628786&partnerID=40>

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This study aimed at examining whether physiological exercise variables at the submaximal level, defined as 75% of the age-predicted target heart rate, are able to predict peak exercise performance in women with chronic fatigue syndrome (CFS) (n = 222). Subjects performed a bicycle ergometric test against a graded increase in workload until exhaustion with continuous monitoring of electrocardiographic and ventilatory variables. Oxygen uptake at the submaximal level (VO₂SUBMAX) correlated strongly with peak oxygen uptake (VO₂PEAK) (r = 0.70). For the prediction of VO₂PEAK, linear regression analysis determined the line of best fit as: VO₂ PEAK = 0.95 \hat{A} — VO₂ SUBMAX + 372.3 .Using this equation, the mean error in the prediction was 14.6 \hat{A} ± 11.2% (range 0.1-63.7%). It is concluded that the prediction of VO₂PEAK based on VO₂SUBMAX might be useful for analyzing group differences or treatment effects but not for individual (clinical) purposes. \hat{A} © 2007 IMSS.

Shevchuk N.A.

Possible use of repeated cold stress for reducing fatigue in chronic fatigue syndrome: A hypothesis

2007 Behavioral and Brain Functions 3

<http://www.scopus.com/inward/record.url?eid=2-s2.0-37849021360&partnerID=40>

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Background: Physiological fatigue can be defined as a reduction in the force output and/or energy-generating capacity of skeletal muscle after exertion, which may manifest itself as an inability to continue exercise or usual activities at the same intensity. A typical example of a fatigue-related disorder is chronic fatigue syndrome (CFS), a disabling condition of unknown etiology and with uncertain therapeutic options. Recent advances in elucidating pathophysiology of this disorder revealed hypofunction of the hypothalamic-pituitary-adrenal axis and that fatigue in CFS patients appears to be associated with reduced motor neurotransmission in the central nervous system (CNS) and to a smaller extent with increased fatigability of skeletal muscle. There is also some limited evidence that CFS patients may have excessive serotonergic activity in the brain and low opioid tone. Presentation of the hypothesis: This work hypothesizes that repeated cold stress may reduce fatigue in CFS because brief exposure to cold may transiently reverse some physiological changes associated with this illness. For example, exposure to cold can activate components of the reticular activating system such as raphe nuclei and locus ceruleus, which can result in activation of behavior and increased capacity of the CNS to recruit motoneurons. Cold stress has also been shown to reduce the level of serotonin in most regions of the brain (except brainstem), which would be consistent with reduced fatigue according to animal models of exercise-related fatigue. Finally, exposure to cold increases metabolic rate and transiently activates the hypothalamic-pituitary-adrenal axis as evidenced by a temporary increase in the plasma levels of adrenocorticotrophic hormone, beta-endorphin and a modest increase in cortisol. The increased opioid tone and high metabolic rate could diminish fatigue by reducing muscle pain and accelerating recovery of fatigued muscle, respectively. Testing the hypothesis: To test the hypothesis, a treatment is proposed that consists of adapted cold showers (20 degrees Celsius, 3 minutes, preceded by a 5-minute gradual adaptation to make the procedure more comfortable) used twice daily. Implications of the hypothesis: If testing supports the proposed hypothesis, this could advance our understanding of the mechanisms of fatigue in CFS. \hat{A} © 2007 Shevchuk; licensee BioMed Central Ltd.

Teitelbaum J.E., Johnson C., St. Cyr J.

The use of D-ribose in chronic fatigue syndrome and fibromyalgia: A pilot study

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Objectives: Fibromyalgia (FMS) and chronic fatigue syndrome (CFS) are debilitating syndromes that are often associated with impaired cellular energy metabolism. As D-ribose has been shown to increase cellular energy synthesis in heart and skeletal muscle, this open-label uncontrolled pilot study was done to evaluate if D-ribose could improve symptoms in fibromyalgia and/or chronic fatigue syndrome patients. **Design:** Forty-one (41) patients with a diagnosis of FMS and/or CFS were given D-ribose, a naturally occurring pentose carbohydrate, at a dose of 5 g t.i.d. for a total of 280 g. All patients completed questionnaires containing discrete visual analog scales and a global assessment pre- and post-D-ribose administration. **Results:** D-ribose, which was well-tolerated, resulted in a significant improvement in all five visual analog scale (VAS) categories: energy; sleep; mental clarity; pain intensity; and well-being, as well as an improvement in patients' global assessment. Approximately 66% of patients experienced significant improvement while on D-ribose, with an average increase in energy on the VAS of 45% and an average improvement in overall well-being of 30% ($p < 0.0001$). **Conclusions:** D-ribose significantly reduced clinical symptoms in patients suffering from fibromyalgia and chronic fatigue syndrome. © Mary Ann Liebert, Inc.

Smith W.R., White P.D., Buchwald D.

A case control study of premorbid and currently reported physical activity levels in chronic fatigue syndrome

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Background: Patients with chronic fatigue syndrome typically report high levels of physical activity before becoming ill. Few studies have examined premorbid and current activity levels in chronically fatigued patients. **Methods:** In a case-control study, 33 patients with chronic, unexplained, disabling fatigue attending a university-based clinic specializing in fatigue were compared to 33 healthy, age- and sex-matched controls. Patients rated their activity levels before their illness and currently, using scales designed for this purpose. Controls reported their level of activity of 2 years previously and currently. Chi-square analyses, Student's t tests, and Wilcoxon signed rank tests were used in pair matched analyses. **Results:** Compared to healthy controls, patients with chronic, unexplained fatigue rated themselves as more active before their illness ($p = 0.001$) and less active currently ($p = 0.001$). The patients also reported they currently stood or walked less than the controls (median [inter-quartile range] = 4 [2-5] versus 9 [7.5-12] hours, $p = 0.001$), and spent more time reclining (median [interquartile range] = 12 [10-16] versus 8 [8-9.5] hours, $p = 0.001$). These differences remained significant for the subset of patients who met strict criteria for chronic fatigue syndrome or fibromyalgia. **Conclusion:** Patients with chronic, unexplained, disabling fatigue reported being more active before becoming ill than healthy controls. This finding could be explained by greater premorbid activity levels that could predispose to illness, or by an overestimation of previous activity. Either possibility could influence patients' perceptions of their current activity levels and their judgments of recovery. Perceived activity should be addressed as part of management of the illness. © 2006 Smith et al; licensee BioMed Central Ltd.

Nijs J., Aerts A., De Meirleir K.

Generalized joint hypermobility is more common in chronic fatigue syndrome than in healthy control subjects

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Objectives: This study aimed at (1) comparing the prevalence of generalized hypermobility in patients with chronic fatigue syndrome (CFS) and healthy volunteers, (2) examining the clinical importance of generalized hypermobility in patients with CFS, and (3) examining whether knee proprioception is associated with hypermobility in patients with CFS. Methods: Sixty-eight patients with CFS filled out two self-reported measures (for the assessment of symptom severity and disability), were questioned about muscle and joint pain, and were screened for generalized hypermobility. Afterward, the patients performed a knee repositioning test (assessment of knee proprioception), and it was examined whether or not they fulfilled the criteria for benign joint hypermobility syndrome (BJHS). Sixty-nine age- and sex-matched healthy volunteers were screened for generalized joint hypermobility and performed the same knee repositioning test. Results: Compared with the healthy volunteers (4.3%, 3/68), significantly more patients with CFS (20.6%, 14/69) fulfilled the criteria for generalized joint hypermobility (Fisher exact test, $P < .004$). No associations were found between generalized joint hypermobility and the self-reported measures (including pain severity) or knee proprioception (Spearman correlation analysis). Knee proprioception was similar in both groups (Mann-Whitney $U = 1961$, $z = -1.745$, $P = .81$). Forty patients with CFS (58.8%) fulfilled the criteria for BJHS. Conclusions: These data indicate that a subgroup of patients with CFS present with generalized joint hypermobility and most patients with of CFS fulfill the diagnostic criteria for BJHS. There appears to be no association between musculoskeletal pain and joint hypermobility in patients with CFS. Copyright © 2006 by National University of Health Sciences.

Wallman K.E., Morton A.R., Goodman C., Grove R.

Exercise prescription for individuals with chronic fatigue syndrome

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[No abstract available]

Schmaling K.B., Fiedelak J.I., Bader J., Buchwald D.

A longitudinal study of physical activity and body mass index among persons with unexplained chronic fatigue

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-21344442153&partnerID=40>

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Objective and Methods: A cohort of 100 patients with unexplained chronic fatigue (CF) was assessed longitudinally for 1.5 years to determine if physical activity (kcal expended), exercise capacity ($VO_2\max$), perceived exertion, and body mass index (BMI) changed over time and were associated

with changes in CF-related clinical status. Results: BMI increased significantly over time but did not predict changes in clinical status. Increasing energy expenditure was associated with increasing vitality and decreasing CF symptom severity over time, and decreasing perceived exertion was associated with increasing physical functioning. However, increasing perceived exertion was also associated with increasing CF symptoms. Conclusions: These data do not support models that posit associations between CF and deconditioning. © 2005 Elsevier Inc. All rights reserved.

Kop W.J., Lyden A., Berlin A.A., Ambrose K., Olsen C., Gracely R.H., Williams D.A., Clauw D.J.
Ambulatory monitoring of physical activity and symptoms in fibromyalgia and chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-12344308876&partnerID=40>

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Objective. Fibromyalgia (FM) and chronic fatigue syndrome (CFS) are associated with substantial physical disability. Determinants of self-reported physical disability are poorly understood. This investigation uses objective ambulatory activity monitoring to compare patients with FM and/or CFS with controls, and examines associations of ambulatory activity levels with both physical function and symptoms during activities of daily life. **Methods.** Patients with FM and/or CFS (n = 38, mean $\bar{A} \pm$ SD age 41.5 $\bar{A} \pm$ 8.2 years, 74% women) completed a 5-day program of ambulatory monitoring of physical activity and symptoms (pain, fatigue, and distress) and results were compared with those in age-matched controls (n = 27, mean $\bar{A} \pm$ SD age 38.0 $\bar{A} \pm$ 8.6 years, 44% women). Activity levels were assessed continuously, ambulatory symptoms were determined using electronically time-stamped recordings at 5 time points during each day, and physical function was measured with the 36-item Short Form health survey at the end of the 5-day monitoring period. **Results.** Patients had significantly lower peak activity levels than controls (mean $\bar{A} \pm$ SEM 8,654 $\bar{A} \pm$ 527 versus 12,913 $\bar{A} \pm$ 1,462 units; P = 0.003) and spent less time in high-level activities when compared with controls (P = 0.001). In contrast, patients had similar average activity levels as those of controls (mean $\bar{A} \pm$ SEM 1,525 $\bar{A} \pm$ 63 versus 1,602 $\bar{A} \pm$ 89; P = 0.47). Among patients, low activity levels were associated with worse self-reported physical function over the preceding month. Activity levels were inversely related to concurrent ambulatory pain (P = 0.031) and fatigue (P < 0.001). Pain and fatigue were associated with reduced subsequent ambulatory activity levels, whereas activity levels were not predictive of subsequent symptoms. **Conclusion.** Patients with FM and/or CFS engaged in less high-intensity physical activities than that recorded for sedentary control subjects. This reduced peak activity was correlated with measures of poor physical function. The observed associations may be relevant to the design of behavioral activation programs, because activity levels appear to be contingent on, rather than predictive of, symptoms.

Jones M.G., Cooper E., Amjad S., Goodwin C.S., Barron J.L., Chalmers R.A.
Urinary and plasma organic acids and amino acids in chronic fatigue syndrome

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Previous work by others have suggested the occurrence of one or more chemical or metabolic 'markers' for ME/CFS including specific amino acids and organic acids and a number of unidentified

compounds (CFSUM1, CFSUM2). We have shown elsewhere that CFSUM1 is partially derivatised pyroglutamic acid and CFSUM2 partially derivatised serine and have suggested and demonstrated that the analytical methods used were unsuitable to identify or to accurately quantify urinary metabolites. We have now made a detailed analysis of plasma and urinary amino acids and of urinary organic acids from patients with ME/CFS and from three control groups. Fasting blood plasma and timed urine samples were obtained from 31 patients with CFS, 31 age and sex-matched healthy controls, 15 patients with depression and 22 patients with rheumatoid arthritis. Plasma and urinary amino acids and urinary organic acids were determined using established and validated methods and data compared by statistical analysis. None of the previously reported abnormalities in urinary amino acids or of organic acids could be confirmed. Results however provide some evidence in patients with ME/CFS for underlying inflammatory disease and for reduced intramuscular collagen with a lowered threshold for muscle micro-injury. These factors in combination may provide a basis for the fatigue and muscle pain that are the major symptoms in these patients. © 2005 Elsevier B.V. All rights reserved.

Jammes Y., Steinberg J.G., Mambrini O., Bregeon F., Delliaux S.
Chronic fatigue syndrome: Assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-14844315700&partnerID=40>

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Objectives. Because the muscle response to incremental exercise is not well documented in patients suffering from chronic fatigue syndrome (CFS), we combined electrophysiological (compound-evoked muscle action potential, M wave), and biochemical (lactic acid production, oxidative stress) measurements to assess any muscle dysfunction in response to a routine cycling exercise. **Design.** This case-control study compared 15 CFS patients to a gender-, age- and weight-matched control group (n = 11) of healthy subjects. **Interventions.** All subjects performed an incremental cycling exercise continued until exhaustion. **Main outcome measures.** We measured the oxygen uptake ($\dot{V}O_2$), heart rate (HR), systemic blood pressure, percutaneous O_2 saturation (SpO_2), M-wave recording from vastus lateralis, and venous blood sampling allowing measurements of pH (pH_v), PO_2 (PvO_2), lactic acid (LA), and three markers of the oxidative stress (thiobarbituric acid-reactive substances, TBARS, reduced glutathione, GSH, and ascorbic acid, RAA). **Results.** Compared with control, in CFS patients (i) the slope of $\dot{V}O_2$ versus work load relationship did not differ from control subjects and there was a tendency for an accentuated PvO_2 fall at the same exercise intensity, indicating an increased oxygen uptake by the exercising muscles; (ii) the HR and blood pressure responses to exercise did not vary; (iii) the anaerobic pathways were not accentuated; (iv) the exercise-induced oxidative stress was enhanced with early changes in TBARS and RAA and enhanced maximal RAA consumption; and (v) the M-wave duration markedly increased during the recovery period. **Conclusions.** The response of CFS patients to incremental exercise associates a lengthened and accentuated oxidative stress together with marked alterations of the muscle membrane excitability. These two objective signs of muscle dysfunction are sufficient to explain muscle pain and postexertional malaise reported by our patients. © 2005 Blackwell Publishing Ltd.

Black C.D., O'Connor P.J., McCully K.K.

Increased daily physical activity and fatigue symptoms in chronic fatigue syndrome

2005 Dynamic Medicine 4

<http://www.scopus.com/inward/record.url?eid=2-s2.0-18044373210&partnerID=40>

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Individuals with chronic fatigue syndrome (CFS) have been shown to have reduced activity levels associated with heightened feelings of fatigue. Previous research has demonstrated that exercise training has beneficial effects on fatigue-related symptoms in individuals with CFS. Purpose: The aim of this study was to sustain an increase in daily physical activity in CFS patients for 4 weeks and assess the effects on fatigue, muscle pain and overall mood. Methods: Six CFS and seven sedentary controls were studied. Daily activity was assessed by a CSA accelerometer. Following a two week baseline period, CFS subjects were asked to increase their daily physical activity by 30% over baseline by walking a prescribed amount each day for a period of four weeks. Fatigue, muscle pain and overall mood were reported daily using a 0 to 100 visual analog scale and weekly using the Profile of Mood States (Bipolar) questionnaire. Results: CFS patients had significantly lower daily activity counts than controls (162.5 \pm 51.7 \pm 103 counts/day vs. 267.2 \pm 79.5 \pm 103 counts/day) during a 2-week baseline period. At baseline, the CFS patients reported significantly ($P < 0.01$) higher fatigue and muscle pain intensity compared to controls but the groups did not differ in overall mood. CFS subjects increased their daily activity by 28 \pm 19.7% over a 4 week period. Overall mood and muscle pain worsened in the CFS patients with increased activity. Conclusion: CFS patients were able to increase their daily physical activity for a period of four weeks. In contrast to previous studies fatigue, muscle pain, and overall mood did not improve with increased activity. Increased activity was not presented as a treatment which may account for the differential findings between this and previous studies. The results suggest that a daily "activity limit" may exist in this population. Future studies on the impact of physical activity on the symptoms of CFS patients are needed. \AA © 2005 Black et al; licensee BioMed Central Ltd.

Black C.D., McCully K.K.

Time course of exercise induced alterations in daily activity in chronic fatigue syndrome

2005 Dynamic Medicine 4

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In a previous study we demonstrated that while people with CFS had lower daily activity levels than control subjects, they were able to increase daily activity via a daily walking program. We reanalyzed our data to determine the time course of activity changes during the walking program. Daily activity assessed via an accelerometer worn at the hip was divided into sleep, active, and walking periods. Over the first 4-10 days of walking the subjects with CFS were able to reach the prescribed activity goals each day. After this time, walking and total activity counts decreased. Sedentary controls subjects were able to maintain their daily walking and total activity goals throughout the 4 weeks. Unlike our previous interpretation of the data, we feel this new analysis suggests that CFS patients may develop exercise intolerance as demonstrated by reduced total activity after 4-10 days. The inability to sustain target activity levels, associated with pronounced worsening of symptomology, suggests the subjects with CFS had reached their activity limit. \AA © 2005 Black and McCully; licensee BioMed Central Ltd.

Bazelmans E., Bleijenberg G., Voeten M.J.M., Van Der Meer J.W.M., Folgering H.

Impact of a maximal exercise test on symptoms and activity in chronic fatigue syndrome

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Objective: This study examined the effects of exercise on symptoms and activity in chronic fatigue syndrome (CFS). Methods: Twenty CFS patients and 20 neighborhood controls performed an incremental exercise test until exhaustion. Fatigue, muscle pain, minutes spent resting, and the level of physical activity were assessed with a self-observation list. Physical activity was assessed with an actometer as well. Data were obtained 3 days before the maximal exercise test (MET) up to 5 days thereafter. Results: For CFS patients, daily observed fatigue was increased up to 2 days after the exercise test. For controls, self-observed fatigue returned to baseline after 2 h. Both CFS patients and controls spent more minutes resting on the day before and on the day after the MET. For CFS patients, self-observed minutes resting increased on the day of the exercise test. For neither group, a decrease of actometer recorded or self-observed physical activity after exercise was found. Conclusion: Fatigue in CFS patients increased after exercise, but the level of actual physical activity remained unchanged. © 2005 Elsevier Inc. All rights reserved.

Wallman K.E., Morton A.R., Goodman C., Grove R.

Physiological responses during a submaximal cycle test in chronic fatigue syndrome

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Introduction/Purpose: Numerous studies have assessed physical function in individuals suffering from chronic fatigue syndrome (CFS) but neglected to match control subjects according to current activity levels, consequently casting doubt on reported results. The purpose of this study was to include current activity levels as one criterion for matching CFS subjects with healthy control subjects in order to more accurately assess physical function in these subjects. Methods: Thirty-one healthy control subjects were matched to CFS subjects according to age, gender, body mass, height, and current activity levels. Physiological function was assessed weekly over a 4-wk period using a submaximal cycle test. Results: Comparison of absolute physiological results recorded at the end of each incremental work level of the exercise test showed that ratings of perceived effort (RPE) was the only variable that was significantly different between the two groups. Scores for RPE were significantly higher in CFS subjects for each incremental work level assessed. Conversely, results recorded on completion of the exercise test showed that the control group was capable of a greater power output than the CFS group as reflected by significantly higher scores for watts per kilogram ($P < 0.0005$), net lactate production ($P = 0.003$), oxygen uptake ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; $P < 0.0005$), respiratory exchange ratio ($P = 0.021$), and HR values as a percentage of age predicted HRmax ($P = 0.001$). End-point RPE scores were again significantly higher in the CFS group ($P < 0.0005$). Conclusion: It is proposed that the reduced exercise tolerance in CFS is due to impairment in the mechanisms that constitute effort sense and/or to avoidance behaviors that result in a reluctance by these subject to exercise to full capacity.

Schillings M.L., Kalkman J.S., Van Der Werf S.P., Van Engelen B.G.M., Bleijenberg G., Zwarts M.J.

Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome

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Objective: We have investigated whether central activation failure (CAF) is increased during local muscle fatigue in chronic fatigue syndrome (CFS). Methods: Fourteen female CFS patients and 14 age-matched healthy female controls made a 2 min sustained maximal voluntary contraction (MVC) of the biceps brachii muscle. Before, during, and after sustained MVC, electrical endplate stimulation was applied. Force and 5 channel surface EMG (sEMG) were registered. Results: Although force responses upon stimulation during rest did not differ between patients and controls, MVC was significantly lower in patients. Already at the beginning of sustained MVC, CFS patients showed significantly larger CAF than controls ($36.5\pm 17.0\%$ and $12.9\pm 13.3\%$, respectively). For all individual patients mean CAF over the first 45 s was higher than 30%, while it was below 30% for all controls. Less peripheral fatigue in patients was demonstrated by the changes in muscle fibre conduction velocity and the differences between force responses before and after contraction. Conclusions: Central activation is diminished in CFS patients. Possible causes include changed perception, impaired concentration, reduced effort and physiologically defined changes, e.g. in the corticospinal excitability or the concentration of neurotransmitters. As a consequence, demands on the muscle are lower, resulting in less peripheral fatigue. Significance: CFS patients show reduced central activation during MVC. The underlying pathophysiological processes remain still to be determined. © 2004 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.

Pendergast D.R., Fisher N.M., Meksawan K., Doubrava M., Vladutiu G.D.

The distribution of white blood cell fat oxidation in health and disease

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-1842538090&partnerID=40>

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Fat oxidation is important for maintaining health and for supplying energy for exercise. We have proposed that the predisposition for individual rates of fat oxidation is determined genetically but may be modulated by acute exercise or exercise training. The purpose of this study was to examine cellular fat oxidation in white blood cells (WBC) using [9, 10-³H]palmitic acid. Sedentary controls free of symptoms (SED-C, n = 32), were compared with known carnitine palmitoyltransferase (CPT) II-deficient patients (n = 2), patients with fatiguing diseases (chronic fatigue syndrome, CFS, n = 6; multiple sclerosis, MS, n = 31), obesity (OB, n = 5), eating disorders (ED, n = 16), sedentary individuals prior to and after exercise (SED-Ex, n = 12), exercise-trained sedentary individuals (SED-Tr, n = 12), and elite runners (ER, n = 5). Fat oxidation in WBC for all subjects was normally distributed (mean = 0.270 ± 0.090 nmol/h per 10⁹ WBC) and ranged from 0.09 nmol/h per 10⁹

WBC in CPT II-deficient patients to 0.59 nmol/h per 109 WBC in ER. There were no significant sex or acute exercise effects on WBC fat oxidation. Patients with MS, OB or ED were not different from SED-C; however, in CPT II-deficient patients, fat oxidation was low, while that of CFS patients was high. Exercise training in SED-C resulted in a 16% increase in fat oxidation but in ER it was still 97% higher than in SED-C. We propose that while WBC fat oxidation is not significantly affected by sex or acute exercise, and only by 15-20% with training, genetic factors play a role in determining both high and low fat oxidation in certain groups of individuals. The genetic predisposition for individual rates of fat oxidation may be easily measured using WBC fat oxidation, as has been shown for CPT II-deficient patients and for elite runners. Ranges of WBC fat oxidation that are abnormally low (<20 nmol/h per 109 WBC, normal 20-35) or high (>35 nmol/h per 109 WBC) are proposed based on genetic factors evaluated in this study. © SSIEM and Kluwer Academic Publishers.

Ohashi K., Bleijenberg G., Van Der Werf S., Prins J., Amaral L.A.N., Natelson B.H., Yamamoto Y.
Decreased Fractal Correlation in Diurnal Physical Activity in Chronic Fatigue Syndrome

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Objectives: Our objectives were to study the temporal correlation of physical activity time series in patients with chronic fatigue syndrome (CFS) during normal daily life and to examine if it could identify the altered physical activity in these patients. Methods: Fractal scoring exponent of diurnal and nocturnal physical activity time series in 10 CFS patients and 6 healthy control subjects (CON) were calculated by the detrended fluctuation analysis (DFA) and the wavelet transform modulus maxima (WTMM) method. We hypothesized that, due to their illness- and/or fatigue-induced resting episodes, altered physical activity patterns in CFS patients might be observed at the interruption of activity bursts. Thus, we further developed a new method, the wavelet transform negative modulus maxima (WTNMM) method, which could evaluate the temporal correlation at the interruption of activities. We compared the fractal scaling exponents for CFS and CON by each method. Results: Both for CFS and CON, we found the fractal time structures in their diurnal physical activity records for at least up to 35 minutes. No group difference was found in nocturnal activities. The WTNMM method revealed that, in diurnal activities, CFS patients had significantly ($p < 0.01$) smaller fractal scaling exponent (0.87 ± 0.03) compared to controls (1.01 ± 0.03). Such a difference was identified neither by the DFA nor WTMM method. Conclusions: CFS patients had more abrupt interruptions of voluntary physical activity during diurnal periods in normal daily life, probed by the decreased correlation in the negative modulus maxima of the wavelet-transformed activity data, possibly due to their exaggerated fatigue.

Nijs J., De Meirleir K., Wolfs S., Duquet W.

Disability evaluation in chronic fatigue syndrome: Association between exercise capacity and activity limitations/participation restrictions

2004 Clinical Rehabilitation 18 (2); 139 - 148

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1542506303&partnerID=40>

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Objective: In an attempt to examine whether impairments in cardiorespiratory fitness are associated with daily functioning in patients with chronic fatigue syndrome (CFS), this study addresses the correlations between exercise capacity and activity limitations/participation restrictions. **Design:** Prospective observational study. **Setting:** An outpatient tertiary care, chronic fatigue clinic at the Vrije Universiteit Brussel (VUB), Belgium. **Subjects:** Seventy-seven patients fulfilling the 1994 Centers for Disease Control and Prevention (CDC) case definition for CFS. **Interventions:** All patients filled in the Chronic Fatigue Syndrome Activities and Participation Questionnaire (CFS-APQ) and performed a maximal exercise stress test on a bicycle ergometer. Heart rate was monitored continuously by use of an electrocardiograph. Metabolic and ventilatory parameters were measured through spirometry. **Results:** A statistically significant correlation between the score obtained with the CFS-APQ and the body weight-adjusted peak oxygen uptake (Spearman $\rho = -0.32$; $p = 0.005$), functional aerobic impairment ($\rho = 0.33$; $p = 0.004$), workload/body weight ($\rho = -0.30$; $p = 0.009$), exercise duration ($\rho = -0.30$; $p = 0.008$), and the percentage of target heart rate achieved ($\rho = -0.33$; $p = 0.004$) was observed. The correlations between the remaining exercise capacity parameters and the scores obtained with the CFS-APQ all indicated a trend towards association ($0.01 < p < 0.05$). **Conclusions:** These results suggest a moderate association between exercise capacity and activity limitations/participation restrictions in patients with CFS. The observed correlations lack strength to predict activity limitations/participation restriction based on exercise capacity parameters. Disability evaluation in CFS should therefore encompass both exercise capacity testing and measurements at the activity/participation dimension. © Arnold 2004.

McCully K.K., Smith S., Rajaei S., Leigh Jr. J.S., Natelson B.H.

Muscle metabolism with blood flow restriction in chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-1342325485&partnerID=40>

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The purpose of this study was to determine whether chronic fatigue syndrome (CFS) is associated with reduced blood flow and muscle oxidative metabolism. Patients with CFS according to Centers for Disease Control criteria ($n = 19$) were compared with normal sedentary subjects ($n = 11$). Muscle blood flow was measured in the femoral artery with Doppler ultrasound after exercise. Muscle metabolism was measured in the medial gastrocnemius muscle with ^{31}P -magnetic resonance spectroscopy. Muscle oxygen saturation and blood volume were measured using near-infrared spectroscopy. CFS and controls were not different in hyperemic blood flow or phosphocreatine recovery rate. Cuff pressures of 50, 60, 70, 80, and 90 mmHg were used to partially restrict blood flow during recovery. All pressures reduced blood flow and oxidative metabolism, with 90 mmHg reducing blood flow by 46% and oxidative metabolism by 30.7% in CFS patients. Hyperemic blood flow during partial cuff occlusion was significantly reduced in CFS patients ($P < 0.01$), and recovery of

oxygen saturation was slower ($P < 0.05$). No differences were seen in the amount of reduction in metabolism with partially reduced blood flow. In conclusion, CFS patients showed evidence of reduced hyperemic flow and reduced oxygen delivery but no evidence that this impaired muscle metabolism. Thus CFS patients might have altered control of blood flow, but this is unlikely to influence muscle metabolism. Furthermore, abnormalities in muscle metabolism do not appear to be responsible for the CFS symptoms.

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Moderate Exercise Increases Expression for Sensory, Adrenergic, and Immune Genes in Chronic Fatigue Syndrome Patients But Not in Normal Subjects

Journal of Pain

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67651218861&partnerID=40>

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Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue, often accompanied by widespread muscle pain that meets criteria for fibromyalgia syndrome (FMS). Symptoms become markedly worse after exercise. Previous studies implicated dysregulation of the sympathetic nervous system (SNS), and immune system (IS) in CFS and FMS. We recently demonstrated that acid sensing ion channel (probably ASIC3), purinergic type 2X receptors (probably P2X4 and P2X5) and the transient receptor potential vanilloid type 1 (TRPV1) are molecular receptors in mouse sensory neurons detecting metabolites that cause acute muscle pain and possibly muscle fatigue. These molecular receptors are found on human leukocytes along with SNS and IS genes. Real-time, quantitative PCR showed that 19 CFS patients had lower expression of β -2 adrenergic receptors but otherwise did not differ from 16 control subjects before exercise. After a sustained moderate exercise test, CFS patients showed greater increases than control subjects in gene expression for metabolite detecting receptors ASIC3, P2X4, and P2X5, for SNS receptors β -2A, β -1, β -2, and COMT and IS genes for IL10 and TLR4 lasting from 0.5 to 48 hours ($P < .05$). These increases were also seen in the CFS subgroup with comorbid FMS and were highly correlated with symptoms of physical fatigue, mental fatigue, and pain. These new findings suggest dysregulation of metabolite detecting receptors as well as SNS and IS in CFS and CFS-FMS. Perspective: Muscle fatigue and pain are major symptoms of CFS. After moderate exercise, CFS and CFS-FMS patients show enhanced gene expression for receptors detecting muscle metabolites and for SNS and IS, which correlate with these symptoms. These findings suggest possible new causes, points for intervention, and objective biomarkers for these disorders. © 2009 American Pain Society.

Genetics and new technological platforms

Lin E., Hsu S.-Y.

A Bayesian approach to gene-gene and gene-environment interactions in chronic fatigue syndrome

2009 Pharmacogenomics 10 (1); 35 - 42

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Introduction: In the study of genomics, it is essential to address gene-gene and gene-environment interactions for describing the complex traits that involves disease-related mechanisms. In this work, our goal is to detect gene-gene and gene-environment interactions resulting from the analysis of chronic fatigue syndrome patients' genetic and demographic factors including SNPs, age, gender and BMI. **Materials & methods:** We employed the dataset that was original to the previous study by the Centers for Disease Control and Prevention Chronic Fatigue Syndrome Research Group. To investigate gene-gene and gene-environment interactions, we implemented a Bayesian based method for identifying significant interactions between factors. Here, we employed a two-stage Bayesian variable selection methodology based on Markov Chain Monte Carlo approaches. **Results:** By applying our Bayesian based approach, NR3C1 was found in the significant two-locus gene-gene effect model, as well as in the significant two-factor gene-environment effect model. Furthermore, a significant gene-environment interaction was identified between NR3C1 and gender. These results support the hypothesis that NR3C1 and gender may play a role in biological mechanisms associated with chronic fatigue syndrome. **Conclusion:** We demonstrated that our Bayesian based approach is a promising method to assess the gene-gene and gene-environment interactions in chronic fatigue syndrome patients by using genetic factors, such as SNPs, and demographic factors such as age, gender and BMI. © 2009 Future Medicine Ltd.

Byrnes A., Jacks A., Dahlman-Wright K., Evengard B., Wright F.A., Pedersen N.L., Sullivan P.F.

Gene expression in peripheral blood leukocytes in monozygotic twins discordant for chronic fatigue: No evidence of a biomarker

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Background: Chronic fatiguing illness remains a poorly understood syndrome of unknown pathogenesis. We attempted to identify biomarkers for chronic fatiguing illness using microarrays to query the transcriptome in peripheral blood leukocytes. **Methods:** Cases were 44 individuals who were clinically evaluated and found to meet standard international criteria for chronic fatigue syndrome or idiopathic chronic fatigue, and controls were their monozygotic co-twins who were clinically evaluated and never had even one month of impairing fatigue. Biological sampling conditions were standardized and RNA stabilizing media were used. These methodological features provide rigorous control for bias resulting from case-control mismatched ancestry and experimental error. Individual gene expression profiles were assessed using Affymetrix Human Genome U133 Plus 2.0 arrays. **Findings:** There were no significant differences in gene expression for any transcript. **Conclusions:** Contrary to our expectations, we were unable to identify a biomarker for chronic fatiguing illness in the transcriptome of peripheral blood leukocytes suggesting that positive findings in prior studies may have resulted from experimental bias. © 2009 Byrnes et al.

Smith A.K., Dimulescu I., Falkenberg V.R., Narasimhan S., Heim C., Vernon S.D., Rajeevan M.S.
Genetic evaluation of the serotonergic system in chronic fatigue syndrome

2008 Psychoneuroendocrinology 33 (2); 188 – 197

<http://www.scopus.com/inward/record.url?eid=2-s2.0-38349121654&partnerID=40>

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Chronic fatigue syndrome (CFS) is a debilitating disorder of unknown etiology with no known lesions, diagnostic markers or therapeutic intervention. The pathophysiology of CFS remains elusive, although abnormalities in the central nervous system (CNS) have been implicated, particularly hyperactivity of the serotonergic (5-hydroxytryptamine; 5-HT) system and hypoactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Since alterations in 5-HT signaling can lead to physiologic and behavioral changes, a genetic evaluation of the 5-HT system was undertaken to identify serotonergic markers associated with CFS and potential mechanisms for CNS abnormality. A total of 77 polymorphisms in genes related to serotonin synthesis (TPH2), signaling (HTR1A, HTR1E, HTR2A, HTR2B, HTR2C, HTR3A, HTR3B, HTR4, HTR5A, HTR6, and HTR7), transport (SLC6A4), and catabolism (MAOA) were examined in 137 clinically evaluated subjects (40 CFS, 55 with insufficient fatigue, and 42 non-fatigued, NF, controls) derived from a population-based CFS surveillance study in Wichita, Kansas. Of the polymorphisms examined, three markers (-1438G/A, C102T, and rs1923884) all located in the 5-HT receptor subtype HTR2A were associated with CFS when compared to NF controls. Additionally, consistent associations were observed between HTR2A variants and quantitative measures of disability and fatigue in all subjects. The most compelling of these associations was with the A allele of -1438G/A (rs6311) which is suggested to have increased promoter activity in functional studies. Further, *in silico* analysis revealed that the -1438 A allele creates a consensus binding site for Th1/E47, a transcription factor implicated in the development of the nervous system. Electrophoretic mobility shift assay supports allele-specific binding of E47 to the A allele but not the G allele at this locus. These data indicate that sequence variation in HTR2A, potentially resulting in its enhanced activity, may be involved in the pathophysiology of CFS.

Saiki T., Kawai T., Morita K., Ohta M., Saito T., Rokutan K., Ban N.

Identification of marker genes for differential diagnosis of chronic fatigue syndrome

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Chronic fatigue syndrome (CFS) is a clinically defined condition characterized by long-lasting disabling fatigue. Because of the unknown mechanism underlying this syndrome, there still is no specific biomarker for objective assessment of the pathological fatigue. We have compared gene expression profiles in peripheral blood between 11 drug-free patients with CFS and age- and sex-matched healthy subjects using a custom microarray carrying complementary DNA probes for 1,467 stress-responsive genes. We identified 12 genes whose mRNA levels were changed significantly in CFS patients. Of these 12 genes, quantitative real-time PCR validated the changes in 9 genes encoding granzyme in activated T or natural killer cells (GZMA), energy regulators (ATP5J2, COX5B, and DBI), proteasome subunits (PSMA3 and PSMA4), putative protein kinase c inhibitor (HINT), GTPase (ARHC), and signal transducers and activators of transcription 5A (STAT5A). Next, we performed the same microarray analysis on 3 additional CFS patients and 20 other patients with the chief complaint of long-lasting fatigue related to other disorders (non-CFS patients) and found that the relative mRNA

expression of 9 genes classified 79% (11/14) of CFS and 85% (17/20) of the non-CFS patients. Finally, real-time PCR measurements of the levels of the 9 involved mRNAs were done in another group of 18 CFS and 12 non-CFS patients. The expression pattern correctly classified 94% (17/18) of CFS and 92% (11/12) of non-CFS patients. Our results suggest that the defined gene cluster (9 genes) may be useful for detecting pathological responses in CFS patients and for differential diagnosis of this syndrome.

Presson A.P., Sobel E.M., Papp J.C., Suarez C.J., Whistler T., Rajeevan M.S., Vernon S.D., Horvath S.
Integrated weighted gene co-expression network analysis with an application to chronic fatigue syndrome

2008 BMC Systems Biology 2

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Background: Systems biologic approaches such as Weighted Gene Co-expression Network Analysis (WGCNA) can effectively integrate gene expression and trait data to identify pathways and candidate biomarkers. Here we show that the additional inclusion of genetic marker data allows one to characterize network relationships as causal or reactive in a chronic fatigue syndrome (CFS) data set. Results: We combine WGCNA with genetic marker data to identify a disease-related pathway and its causal drivers, an analysis which we refer to as "Integrated WGCNA" or IWGCNA. Specifically, we present the following IWGCNA approach: 1) construct a co-expression network, 2) identify trait-related modules within the network, 3) use a trait-related genetic marker to prioritize genes within the module, 4) apply an integrated gene screening strategy to identify candidate genes and 5) carry out causality testing to verify and/or prioritize results. By applying this strategy to a CFS data set consisting of microarray, SNP and clinical trait data, we identify a module of 299 highly correlated genes that is associated with CFS severity. Our integrated gene screening strategy results in 20 candidate genes. We show that our approach yields biologically interesting genes that function in the same pathway and are causal drivers for their parent module. We use a separate data set to replicate findings and use Ingenuity Pathways Analysis software to functionally annotate the candidate gene pathways. Conclusion: We show how WGCNA can be combined with genetic marker data to identify disease-related pathways and the causal drivers within them. The systems genetics approach described here can easily be used to generate testable genetic hypotheses in other complex disease studies. © 2008 Presson et al; licensee BioMed Central Ltd.

Kerr J.R., Petty R., Burke B., Gough J., Fear D., Sinclair L.I., Matthey D.L., Richards S.C.M., Montgomery J., Baldwin D.A., Kellam P., Harrison T.J., Griffin G.E., Main J., Enlander D., Nutt D.J., Holgate S.T.

Gene expression subtypes in patients with chronic fatigue syndrome/myalgic encephalomyelitis

2008 Journal of Infectious Diseases 197 (8); 1171 – 1184

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Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a multisystem disease, the pathogenesis of which remains undetermined. We set out to determine the precise abnormalities of gene expression in the blood of patients with CFS/ME. We analyzed gene expression in peripheral blood from 25 patients with CFS/ME diagnosed according to the Centers for Disease Control and Prevention diagnostic criteria and 50 healthy blood donors, using a microarray with a cutoff fold difference of expression of ≥ 2.5 . Genes showing differential expression were further analyzed in 55 patients with CFS/ME and 75 healthy blood donors, using quantitative polymerase chain reaction. Differential expression was confirmed for 88 genes; 85 were upregulated, and 3 were downregulated. Highly represented functions were hematological disease and function, immunological disease and function, cancer, cell death, immune response, and infection. Clustering of quantitative polymerase chain reaction data from patients with CFS/ME revealed 7 subtypes with distinct differences in Medical Outcomes Survey Short Form-36 scores, clinical phenotypes, and severity. © 2008 by the Infectious Diseases Society of America. All rights reserved.

Kerr J.R., Burke B., Petty R., Gough J., Fear D., Matthey D.L., Axford J.S., Dalglish A.G., Nutt D.J. Seven genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis: A detailed analysis of gene networks and clinical phenotypes

2008 Journal of Clinical Pathology 61 (6); 730 – 739

<http://www.scopus.com/inward/record.url?eid=2-s2.0-45549102593&partnerID=40>

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Aim: Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a multisystem disease, the pathogenesis of which remains undetermined. The authors have recently reported a study of gene expression that identified differential expression of 88 human genes in patients with CFS/ME. Clustering of quantitative PCR (qPCR) data from patients with CFS/ME revealed seven distinct subtypes with distinct differences in Medical Outcomes Survey Short Form-36 scores, clinical phenotypes and severity. **Methods:** In this study, for each CFS/ME subtype, those genes whose expression differed significantly from that of normal blood donors were identified, and then gene interactions, disease associations and molecular and cellular functions of those gene sets were determined. Genomic analysis was then related to clinical data for each CFS/ME subtype. **Results:** Genomic analysis revealed some common (neurological, haematological, cancer) and some distinct (metabolic, endocrine, cardiovascular, immunological, inflammatory) disease associations among the subtypes. Subtypes 1, 2 and 7 were the most severe, and subtype 3 was the mildest. Clinical features of each subtype were as follows: subtype 1 (cognitive, musculoskeletal, sleep, anxiety/depression); subtype 2 (musculoskeletal, pain, anxiety/depression); subtype 3 (mild); subtype 4 (cognitive); subtype 5 (musculoskeletal, gastrointestinal); subtype 6 (postexertional); subtype 7 (pain, infectious, musculoskeletal, sleep, neurological, gastrointestinal, neurocognitive, anxiety/depression). **Conclusion:** It was particularly interesting that in the seven genomically derived subtypes there were distinct clinical syndromes, and that those which were most severe were also those with anxiety/depression, as would be expected in a disease with a biological basis.

Kennedy P., Simoff S.J., Catchpoole D.R., Skillicorn D.B., Ubaudi F., Al-Oqaily A.
Integrative visual data mining of biomedical data: Investigating cases in Chronic Fatigue Syndrome and Acute Lymphoblastic Leukaemia

2008 Lecture Notes in Computer Science 4404; 367 – 388

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This chapter presents an integrative visual data mining approach towards biomedical data. This approach and supporting methodology are presented at a high level. They combine in a consistent manner a set of visualisation and data mining techniques that operate over an integrated data set of several diverse components, including medical (clinical) data, patient outcome and interview data, corresponding gene expression and SNP data, domain ontologies and health management data. The practical application of the methodology and the specific data mining techniques engaged are demonstrated on two case studies focused on the biological mechanisms of two different types of diseases: Chronic Fatigue Syndrome and Acute Lymphoblastic Leukaemia, respectively. The common between the cases is the structure of the data sets. © 2008 Springer-Verlag Berlin Heidelberg.

Grans H., Evengard B., Nilsson P.

Transcriptome analysis of peripheral blood mononuclear cells from patients with chronic fatigue syndrome

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Objective: Chronic fatigue syndrome (CFS) is an illness defined by unexplained disabling fatigue lasting longer than six months, together with at least four out of eight specified symptoms. The etiology and pathophysiology of CFS are to a large degree unknown. Since much remains unclear about CFS we wanted to investigate transcript expression levels in peripheral blood mononuclear cells to identify genes that are involved in CFS. Method: Transcript expression profiles for 20 CFS patients were compared with 14 healthy controls using microarray technology. Results were verified with real-time PCR. Results: We have identified significantly differentially expressed genes comparing a female CFS patient subgroup with gradual illness onset and no previously documented infection with female healthy controls. We have also created a list of genes with indicated, but not verified, expression differences from comparisons between other subgroups and healthy controls. These genes are candidates for further study of potential involvement in CFS. Conclusion: Our results stress the necessity of subgrouping the heterogeneous CFS patient cohort. The mRNA expression differences identified here may be causal factors for the illness or symptoms observed in these patients, or a result of altered functions of other cellular components involved in the illness. The role of these genes in the CFS pathology needs further investigation. Copyright © by The Haworth Press, Inc. All rights reserved.

Garcia-Fructuoso F.J., Lao-Villadoniga J.I., Santos C., Poca-Dias V., Fernandez-Sola J.
Identification of differential genetic profiles in severe forms of fibromyalgia and chronic fatigue syndrome/myalgic encephalomyelitis: A population-based genetic association study

2008 Journal of Clinical Research 11 (Jan-24); 1 – 24

<http://www.scopus.com/inward/record.url?eid=2-s2.0-43749102463&partnerID=40>

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Background: Fibromyalgia (FM) and chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) are believed to be two separate illnesses that are diagnosed using separate but overlapping clinical criteria; to date there are no biological markers for either condition. The symptoms of both disorders can differ markedly in presentation, frequency and intensity and therefore it is necessary to distinguish between the subtypes. Since recent studies have begun to determine the genetic background of these diseases, the authors suggest the use of single nucleotide polymorphism (SNP) analysis to investigate their different genetic profiles. Methods: A group of 403 women (186 FM and 217 CFS/ME) were recruited for the study using the American College of Rheumatology 1990 and the US Centers for Disease Control and Prevention (CDC) research definition for FM and CFS diagnosis criteria, respectively. The Fibromyalgia Impact Questionnaire and the CDC Symptom Inventory questionnaires were used to define severity subgroups. For each sample, 107 SNPs were genotyped by SNPlex[®]. An independent second association study with 282 women (126 FM and 156 CFS/ME) was used to validate the results. Results: Fifteen SNPs were identified that were able to discriminate between FM and CFS patients with a likelihood ratio (LR+) of 11.5 (95% specificity). Analysis of further SNPs allowed differential genetic profiling between the most aggressive FM phenotype and the mild forms (LR+ 12.4) and between a severe CFS/ME phenotype and a milder one (LR+ 12.4). Conclusions: In this study, the authors claim that FM and CFS/ME are, at least in a subgroup of patients, two separate diseases with an important genetic component and suggest that CFS/ME diagnosis should be an exclusion criterion for FM diagnosis. In addition, severe cases might be different disease subtypes with distinctive genetic profiles. © 2008 Informa UK Ltd.

Emmert-Streib F.

The chronic fatigue syndrome: A comparative pathway analysis

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-34548747580&partnerID=40>

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In this paper, we introduce a method to detect pathological pathways of a disease. We aim to identify biological processes rather than single genes affected by the chronic fatigue syndrome (CFS). So far, CFS has neither diagnostic clinical signals nor abnormalities that could be diagnosed by laboratory examinations. It is also unclear if the CFS represents one disease or can be subdivided in different categories. We use information from clinical trials, the gene ontology (GO) database as well as gene expression data to identify undirected dependency graphs (UDGs) representing biological processes according to the GO database. The structural comparison of UDGs of sick versus non-sick patients allows us to make predictions about the modification of pathways due to pathogenesis. © Mary Ann Liebert, Inc.

Chung Y., Lee S.Y., Elston R.C., Park T.

Odds ratio based multifactor-dimensionality reduction method for detecting gene - Gene interactions

2007 *Bioinformatics* 23 (1); 71 - 76

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33845903040&partnerID=40>

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Motivation: The identification and characterization of genes that increase the susceptibility to common complex multifactorial diseases is a challenging task in genetic association studies. The multifactor dimensionality reduction (MDR) method has been proposed and implemented by Ritchie et al. (2001) to identify the combinations of multilocus genotypes and discrete environmental factors that are associated with a particular disease. However, the original MDR method classifies the combination of multilocus genotypes into high-risk and low-risk groups in an ad hoc manner based on a simple comparison of the ratios of the number of cases and controls. Hence, the MDR approach is prone to false positive and negative errors when the ratio of the number of cases and controls in a combination of genotypes is similar to that in the entire data, or when both the number of cases and controls is small. Hence, we propose the odds ratio based multifactor dimensionality reduction (OR MDR) method that uses the odds ratio as a new quantitative measure of disease risk. Results: While the original MDR method provides a simple binary measure of risk, the OR MDR method provides not only the odds ratio as a quantitative measure of risk but also the ordering of the multilocus combinations from the highest risk to lowest risk groups. Furthermore, the OR MDR method provides a confidence interval for the odds ratio for each multilocus combination, which is extremely informative in judging its importance as a risk factor. The proposed OR MDR method is illustrated using the dataset obtained from the CDC Chronic Fatigue Syndrome Research Group. © 2007 Oxford University Press.

Waltman P., Pearlman A., Mishra B.

Interpreter of maladies: Redescription mining applied to biomedical data analysis

2006 *Pharmacogenomics* 7 (3); 503 - 509

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646063824&partnerID=40>

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Comprehensive, systematic and integrated data-centric statistical approaches to disease modeling can provide powerful frameworks for understanding disease etiology. Here, one such computational framework based on redescription mining in both its incarnations, static and dynamic, is discussed. The static framework provides bioinformatic tools applicable to multifaceted datasets, containing genetic, transcriptomic, proteomic, and clinical data for diseased patients and normal subjects. The dynamic redescription framework provides systems biology tools to model complex sets of regulatory, metabolic and signaling pathways in the initiation and progression of a disease. As an example, the case of chronic fatigue syndrome (CFS) is considered, which has so far remained intractable and unpredictable in its etiology and nosology. The redescription mining approaches can be applied to the Centers for Disease Control and Prevention's Wichita (KS, USA) dataset, integrating transcriptomic, epidemiological and clinical data, and can also be used to study how pathways in the hypothalamic-pituitary-adrenal axis affect CFS patients. © 2006 Future Medicine Ltd.

Smith A.K., White P.D., Aslakson E., Vollmer-Connor U., Rajeevan M.S.

Polymorphisms in genes regulating the HPA axis associated with empirically delineated classes of unexplained chronic fatigue

2006 Pharmacogenomics 7 (3); 387 - 394

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Chronic fatigue syndrome (CFS) is characterized by persistent or relapsing fatigue that is not alleviated by rest, causes substantial reduction in activities and is accompanied by a variety of symptoms. Its unknown etiology may reflect that CFS is heterogeneous. Latent class analyses of symptoms and physiological systems were used to delineate subgroups within a population-based sample of fatigued and nonfatigued subjects [1]. This study examined whether genetic differences underlie the individual subgroups of the latent class solution. Polymorphisms in 11 candidate genes related to both hypothalamic-pituitary-adrenal (HPA) axis function and mood-related neurotransmitter systems were evaluated by comparing each of the five ill classes (Class 1, n = 33; Class 3, n = 22; Class 4, n = 22; Class 5, n = 17; Class 6, n = 11) of fatigued subjects with subjects defined as well (Class 2, n = 35). Of the five classes of subjects with unexplained fatigue, three classes were distinguished by gene polymorphisms involved in either HPA axis function or neurotransmitter systems, including proopiomelanocortin (POMC), nuclear receptor subfamily 3, group C, member 1 (NR3C1), monoamine oxidase A (MAOA), monoamine oxidase B (MAOB), and tryptophan hydroxylase 2 (TPH2). These data support the hypothesis that medically unexplained chronic fatigue is heterogeneous and presents preliminary evidence of the genetic mechanisms underlying some of the putative conditions. © 2006 Future Medicine Ltd.

Sakudo A., Kuratsune H., Kobayashi T., Tajima S., Watanabe Y., Ikuta K.

Spectroscopic diagnosis of chronic fatigue syndrome by visible and near-infrared spectroscopy in serum samples

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33744508318&partnerID=40>

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To investigate visible and near-infrared (Vis-NIR) spectroscopy enabling chronic fatigue syndrome (CFS) diagnosis, we subjected sera from CFS patients as well as healthy donors to Vis-NIR spectroscopy. Vis-NIR spectra in the 600-1100 nm region for sera from 77 CFS patients and 71 healthy donors were subjected to principal component analysis (PCA) and soft independent modeling of class analogy (SIMCA) to develop multivariate models to discriminate between CFS patients and healthy donors. The model was further assessed by the prediction of 99 masked other determinations (54 in the healthy group and 45 in the CFS patient group). The PCA model predicted successful discrimination of the masked samples. The SIMCA model predicted 54 of 54 (100%) healthy donors and 42 of 45 (93.3%) CFS patients of Vis-NIR spectra from masked serum samples correctly. These results suggest that Vis-NIR spectroscopy for sera combined with chemometrics analysis could provide a promising tool to objectively diagnose CFS. © 2006 Elsevier Inc. All rights reserved.

Kaiser J.

Biomedicine. Genes and chronic fatigue: how strong is the evidence?

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646679126&partnerID=40>

[No abstract available]

Gurbaxani B.M., Jones J.F., Goertzel B.N., Maloney E.M.

Linear data mining the Wichita clinical matrix suggests sleep and allostatic load involvement in chronic fatigue syndrome

2006 Pharmacogenomics 7 (3); 455 - 465

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646027306&partnerID=40>

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Objectives: To provide a mathematical introduction to the Wichita (KS, USA) clinical dataset, which is all of the nongenetic data (no microarray or single nucleotide polymorphism data) from the 2-day clinical evaluation, and show the preliminary findings and limitations, of popular, matrix algebra-based data mining techniques. Methods: An initial matrix of 440 variables by 227 human subjects was reduced to 183 variables by 164 subjects. Variables were excluded that strongly correlated with chronic fatigue syndrome (CFS) case classification by design (for example, the multidimensional fatigue inventory [MFI] data), that were otherwise self reporting in nature and also tended to correlate strongly with CFS classification, or were sparse or nonvarying between case and control. Subjects were excluded if they did not clearly fall into well-defined CFS classifications, had comorbid depression with melancholic features, or other medical or psychiatric exclusions. The popular data mining techniques, principle components analysis (PCA) and linear discriminant analysis (LDA), were used to determine how well the data separated into groups. Two different feature selection methods helped identify the most discriminating parameters. Results: Although purely biological features (variables) were found to separate CFS cases from controls, including many allostatic load and sleep-related variables, most parameters were not statistically significant individually. However, biological correlates of CFS, such as heart rate and heart rate variability, require further investigation. Conclusions: Feature selection of a limited number of variables from the purely biological dataset produced better separation between groups than a PCA of the entire dataset. Feature selection highlighted the importance of many of the allostatic load variables studied in more detail by Maloney and colleagues in this issue [1], as well as some sleep-related variables. Nonetheless, matrix linear algebra-based data mining approaches appeared to be of limited utility when compared with more sophisticated nonlinear analyses on richer data types, such as those found in Maloney and colleagues [1] and Goertzel and colleagues [2] in this issue. © 2006 Future Medicine Ltd.

Goertzel B.N., Pennachin C., de Souza Coelho L., Gurbaxani B., Maloney E.M., Jones J.F.

Combinations of single nucleotide polymorphisms in neuroendocrine effector and receptor genes predict chronic fatigue syndrome

2006 Pharmacogenomics 7 (3); 475 - 483

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646070585&partnerID=40>

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Objective: This paper asks whether the presence of chronic fatigue syndrome (CFS) can be more accurately predicted from single nucleotide polymorphism (SNP) profiles than would occur by chance. Methods: Specifically, given SNP profiles for 43 CFS patients, together with 58 controls, we used an enumerative search to identify an ensemble of conjunctive rules that predict whether a patient has

CFS. Results: The accuracy of the rules reached 76.3%, with the highest accuracy rules yielding 49 true negatives, 15 false negatives, 28 true positives and nine false positives (odds ratio [OR] 8.94, $p < 0.0001$). Analysis of the SNPs used most frequently in the overall ensemble of rules gave rise to a list of 'most important SNPs', which was not identical to the list of 'most differentiating SNPs' that one would calculate via studying each SNP independently. The top three genes containing the SNPs accounting for the highest accumulated importances were neuronal tryptophan hydroxylase (TPH2), catechol-O-methyltransferase (COMT) and nuclear receptor subfamily 3, group C, member 1 glucocorticoid receptor (NR3C1). Conclusion: The fact that only 28 out of several million possible SNPs predict whether a person has CFS with 76% accuracy indicates that CFS has a genetic component that may help to explain some aspects of the illness. © 2006 Future Medicine Ltd.

Fostel J., Boneva R., Lloyd A.

Exploration of the gene expression correlates of chronic unexplained fatigue using factor analysis

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646027896&partnerID=40>

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Objective: To identify biomarkers of chronic fatigue syndrome (CFS) and related disorders through analysis of microarray data, pathology test results and self-report symptom profiles. Method: To empirically derive the symptom domains of the illnesses, factor analysis was performed on responses to self-report questionnaires (multidimensional fatigue inventory, Centers for Disease Control and Prevention (CDC) symptom inventory and Zung depression scale) before validation with independent datasets. Gene expression patterns that distinguished subjects across each factor dimension were then sought. Results: A four-factor solution was favored, featuring 'fatigue' and 'mood disturbance' factors. Scores on these factors correlated with measures of disability on the Short Form (SF)-36. A total of 57 genes that distinguished subjects along each factor dimension were identified, although the separation was significant only for subjects beyond the extreme (15th and 85th) percentiles of severity. Clustering of laboratory parameters with expression of these genes revealed associations with serum measurements of pH, electrolytes, glucose, urea, creatinine, and liver enzymes (aspartate amino transferase [AST] and alanine amino transferase [ALT]); as well as hematocrit and white cell count. Conclusion: CFS is a complex syndrome that cannot simply be associated with changes in individual laboratory tests or expression levels of individual genes. No clear association with gene expression and individual symptom domains was found. However, analysis of such multifaceted datasets is likely to be an important means to elucidate the pathogenesis of CFS. © 2006 Future Medicine Ltd.

Fang H., Xie Q., Boneva R., Fostel J., Perkins R., Tong W.

Gene expression profile exploration of a large dataset on chronic fatigue syndrome

2006 Pharmacogenomics 7 (3); 429 - 440

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646025251&partnerID=40>

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Objective: To gain understanding of the molecular basis of chronic fatigue syndrome (CFS) through gene expression analysis using a large microarray data set in conjunction with clinically administered questionnaires. Method: Data from the Wichita (KS,USA) CFS Surveillance Study was used, comprising 167 participants with two self-report questionnaires (multidimensional fatigue inventory

[MFI] and Zung depression scale [Zung]), microarray data, empiric classification, and others. Microarray data was analyzed using bioinformatics tools from ArrayTrack. Results: Correspondence analysis was applied to the MFI questionnaire to select the 23 samples having either the most or the least fatigue, and to the Zung questionnaire to select the 26 samples having either the most or least depression; ten samples were common, resulting in a total of 39 samples. The MFI and Zung-based CFS/non-CFS (NF) classifications on the 39 samples were consistent with the empiric classification. Two differentially-expressed gene lists were determined, 188 fatigue-related genes and 164 depression-related genes, which shared 24 common genes and involved 11 common pathways. Principal component analysis based on 24 genes clearly separates 39 samples with respect to their likelihood to be CFS. Most of the 24 genes are not previously reported for CFS, yet their functions are consistent with the prevailing model of CFS, such as immune response, apoptosis, ion channel activity, signal transduction, cell-cell signaling, regulation of cell growth and neuronal activity. Hierarchical cluster analysis was performed based on 24 genes to classify 128 (=167-39) unassigned samples. Several of the 11 identified common pathways are supported by earlier findings for CFS, such as cytokine-cytokine receptor interaction and neuroactive ligand-receptor interaction. Importantly, most of the 11 common pathways are interrelated, suggesting complex biological mechanisms associated with CFS. Conclusion: Bioinformatics is critical in this study to select definitive sample groups, analyze gene expression data and gain insight into biological mechanisms. The 24 identified common genes and 11 common pathways could be important in future studies of CFS at the molecular level. © 2006 Future Medicine Ltd.

Craddock R.C., Taylor R., Broderick G., Whistler T., Klimas N., Unger E.R.

Exploration of statistical dependence between illness parameters using the entropy correlation coefficient

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The entropy correlation coefficient (ECC) is a useful tool for measuring statistical dependence between variables. We employed this tool to search for pairs of variables that correlated in the chronic fatigue syndrome (CFS) Computational Challenge dataset. Highly related variables are candidates for data reduction, and novel relationships could lead to hypotheses regarding the pathogenesis of CFS. Methods: Data for 130 female participants in the Wichita (KS, USA) clinical study [1] was coded into numerical values. Metric data was grouped using Gaussian mixture models; the number of groups was chosen using Bayesian information content. The pair-wise correlation between all variables was computed using the ECC. Significance was estimated from 1000 iterations of a permutation test and a threshold of 0.01 was used to identify significantly correlated variables. Results: The five dimensions of multidimensional fatigue inventory (MFI) were all highly correlated with each other. Seven Short Form (SF)-36 measures, four CFS case-defining symptoms and the Zung self-rating depression scale all correlated with all MFI dimensions. No physiological variables correlate with more than one MA dimension. MFI, SF-36, CDC symptom inventory, the Zung self-rating depression scale and three Cambridge Neuropsychological Test Automated Battery (CANTAB) measures are highly correlated with CFS disease status. Discussion: Correlations between the five dimensions of MFI are expected since they are measured from the same instrument. The relationship between MFI and Zung depression index has been previously reported. MFI, SF-36, and Centers for Disease Control and Prevention (CDC) symptom inventory are used to classify CFS; it is not surprising that they are correlated with disease status. Only one of the three CANTAB measures that correlate with disease status has been previously found, indicating the ECC identifies relationships not found with other statistical tools. Conclusion: The ECC is a useful tool for measuring statistical dependence between variables in clinical and laboratory datasets. The ECC needs to be further studied to gain a better understanding of its meaning for clinical data. © 2006 Future Medicine Ltd.

Carmel L., Efroni S., White P.D., Aslakson E., Vollmer-Conna U., Rajeevan M.S.
Gene expression profile of empirically delineated classes of unexplained chronic fatigue

2006 Pharmacogenomics 7 (3); 375 - 386

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646019568&partnerID=40>

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Objectives: To identify the underlying gene expression profiles of unexplained chronic fatigue subjects classified into five or six class solutions by principal component (PCA) and latent class analyses (LCA). Methods: Microarray expression data were available for 15,315 genes and 111 female subjects enrolled from a population-based study on chronic fatigue syndrome. Algorithms were developed to assign gene scores and threshold values that signified the contribution of each gene to discriminate the multiclass in each LCA solution. Unsupervised dimensionality reduction was first used to remove noise or otherwise uninformative gene combinations, followed by supervised dimensionality reduction to isolate gene combinations that best separate the classes. Results: The authors' gene score and threshold algorithms identified 32 and 26 genes capable of discriminating the five and six multiclass solutions, respectively. Pair-wise comparisons suggested that some genes (zinc finger protein 350 [ZNF350], solute carrier family 1, member 6 [SLC1A6], F-box protein 7 [FBX07] and vacuole 14 protein homolog [VAC14]) distinguished most classes of fatigued subjects from healthy subjects, whereas others (patched homolog 2 [PTCH2] and T-cell leukemia/ lymphoma [TCL1A]) differentiated specific fatigue classes. Conclusion: A computational approach was developed for general use to identify discriminatory genes in any multiclass problem. Using this approach, differences in gene expression were found to discriminate some classes of unexplained chronic fatigue, particularly one termed interoception. © 2006 Future Medicine Ltd.

Carlo-Stella N., Badulli C., De Silvestri A., Bazzichi L., Martinetti M., Lorusso L., Bombardieri S., Salvaneschi L., Cuccia M.

A first study of cytokine genomic polymorphisms in CFS: Positive association of TNF-857 and IFN γ 874 rare alleles

2006 Clinical and Experimental Rheumatology 24 (2); 179 – 182

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33744786248&partnerID=40>

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Objective. In the past two years we have developed a biological bank of genomic DNA, cDNA, serum and red blood cells of Italian patients with certified CFS from the two Italian referral centers for the syndrome. Recent studies have shown an imbalance in cytokine production in disease states similar to Chronic Fatigue Syndrome (CFS), such as sickness behavior, both in animals and in humans. However we notice that serum cytokine concentrations are often inconstant and degrade rapidly. With this in mind, we investigated cytokine gene polymorphisms in 80 Italian patients with CFS in order to ascertain whether in this group of patients it is possible to describe a genetic predisposition to an inflammatory response. Methods. We analyzed the promoter polymorphisms of IL-10, IL-6 and the IFN γ 874 T/A polymorphism in intron 1 with a PCR-SSP method (Cytogen One Lambda Inc. Canoga Park, CA, U.S.A) in 54 patients and TNF-308 G/A and -857 C/T promoter polymorphisms with a PCR-RFLP method (in 54 and 80 patients respectively). Results. There is a highly significant increase of TNF-857 TT and CT genotypes ($p = 0.002$) among patients with respect to controls and a significant decrease of IFN gamma low producers (A/A) ($p = 0.04$) among patients with respect to controls. Conclusions. We hypothesize that CFS patients can have a genetic predisposition to an immunomodulatory response of an inflammatory nature probably secondary to one or more

environmental insults of unknown nature. © Copyright Clinical and Experimental Rheumatology 2006.

Whistler T., Jones J.F., Unger E.R., Vernon S.D.

Exercise responsive genes measured in peripheral blood of women with Chronic Fatigue Syndrome and matched control subjects

2005 BMC Physiology 5

<http://www.scopus.com/inward/record.url?eid=2-s2.0-17844367577&partnerID=40>

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Background: Chronic fatigue syndrome (CFS) is defined by debilitating fatigue that is exacerbated by physical or mental exertion. To search for markers of CFS-associated post-exertional fatigue, we measured peripheral blood gene expression profiles of women with CFS and matched controls before and after exercise challenge. Results: Women with CFS and healthy, age-matched, sedentary controls were exercised on a stationary bicycle at 70% of their predicted maximum workload. Blood was obtained before and after the challenge, total RNA was extracted from mononuclear cells, and signal intensity of the labeled cDNA hybridized to a 3800-gene oligonucleotide microarray was measured. We identified differences in gene expression among and between subject groups before and after exercise challenge and evaluated differences in terms of Gene Ontology categories. Exercise-responsive genes differed between CFS patients and controls. These were in genes classified in chromatin and nucleosome assembly, cytoplasmic vesicles, membrane transport, and G protein-coupled receptor ontologies. Differences in ion transport and ion channel activity were evident at baseline and were exaggerated after exercise, as evidenced by greater numbers of differentially expressed genes in these molecular functions. Conclusion: These results highlight the potential use of an exercise challenge combined with microarray gene expression analysis in identifying gene ontologies associated with CFS. © 2005 Whistler et al; licensee BioMed Central Ltd.

Smith J., Fritz E.L., Kerr J.R., Cleare A.J., Wessely S., Matthey D.L.

Association of chronic fatigue syndrome with human leucocyte antigen class II alleles

2005 Journal of Clinical Pathology 58 (8); 860 – 863

<http://www.scopus.com/inward/record.url?eid=2-s2.0-23444460688&partnerID=40>

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Background: A genetic component to the development of chronic fatigue syndrome (CFS) has been proposed, and a possible association between human leucocyte antigen (HLA) class II antigens and chronic fatigue immune dysfunction has been shown in some, but not all, studies. Aims: To investigate the role of HLA class II antigens in CFS. Methods: Forty nine patients with CFS were genotyped for the HLA-DRB1, HLA-DQA1, and HLA-DQB1 alleles and the frequency of these alleles was compared with a control group comprising 102 normal individuals from the UK. All patients and controls were from the same region of England and, apart from two patients, were white. Results: Analysis by 2 × 2 contingency tables revealed an increased frequency of HLA-DQA1*01 alleles in patients with CFS (51.0% v 35%; odds ratio (OR), 1.93; p = 0.008). HLA-DQB1*06 was also increased in the patients with CFS (30.2% v 20.0%; OR, 1.73, p = 0.052). Only the association between HLA-DQA1*01 and CFS was significant in logistic regression models containing HLA-

DQA1*01 and HLA-DRQB1*06, and this was independent of HLA-DRB1 alleles. There was a decreased expression of HLA-DRB1*11 in CFS, although this association disappeared after correction for multiple comparisons. Conclusions: CFS may be associated with HLA-DQA1*01, although a role for other genes in linkage disequilibrium cannot be ruled out.

Kaushik N., Fear D., Richards S.C.M., McDermott C.R., Nuwaysir E.F., Kellam P., Harrison T.J., Wilkinson R.J., Tyrrell D.A.J., Holgate S.T., Kerr J.R.

Gene expression in peripheral blood mononuclear cells from patients with chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-23444442051&partnerID=40>

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Background: Chronic fatigue syndrome (CFS) is a multisystem disease, the pathogenesis of which remains undetermined. Aims: To test the hypothesis that there are reproducible abnormalities of gene expression in patients with CFS compared with normal healthy persons. Methods: To gain further insight into the pathogenesis of this disease, gene expression was analysed in peripheral blood mononuclear cells from 25 patients with CFS diagnosed according to the Centers for Disease Control criteria and 25 normal blood donors matched for age, sex, and geographical location, using a single colour microarray representing 9522 human genes. After normalisation, average difference values for each gene were compared between test and control groups using a cutoff fold difference of expression ≥ 1.5 and a p value of 0.001. Genes showing differential expression were further analysed using Taqman real time polymerase chain reaction (PCR) in fresh samples. Results: Analysis of microarray data revealed differential expression of 35 genes. Real time PCR confirmed differential expression in the same direction as array results for 16 of these genes, 15 of which were upregulated (ABCD4, PRKCL1, MRPL23, CD2BP2, GSN, NTE, POLR2G, PEX16, EIF2B4, EIF4G1, ANAPC11, PDCD2, KHSRP, BRMS1, and GABARAPL1) and one of which was downregulated (IL-10RA). This profile suggests T cell activation and perturbation of neuronal and mitochondrial function. Upregulation of neuropathy target esterase and eukaryotic translation initiation factor 4G1 may suggest links with organophosphate exposure and virus infection, respectively. Conclusion: These results suggest that patients with CFS have reproducible alterations in gene regulation.

Baraniuk J.N., Casado B., Maibach H., Clauw D.J., Pannell L.K., Hess S.

A chronic fatigue syndrome - Related proteome in human cerebrospinal fluid

2005 BMC Neurology 5

<http://www.scopus.com/inward/record.url?eid=2-s2.0-29144442160&partnerID=40>

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Background: Chronic Fatigue Syndrome (CFS), Persian Gulf War Illness (PGI), and fibromyalgia are overlapping symptom complexes without objective markers or known pathophysiology. Neurological dysfunction is common. We assessed cerebrospinal fluid to find proteins that were differentially expressed in this CFS-spectrum of illnesses compared to control subjects. **Methods:** Cerebrospinal fluid specimens from 10 CFS, 10 PGI, and 10 control subjects (50 μ l/subject) were pooled into one sample per group (cohort 1). Cohort 2 of 12 control and 9 CFS subjects had their fluids (200 μ l/subject) assessed individually. After trypsin digestion, peptides were analyzed by capillary chromatography, quadrupole-time-of-flight mass spectrometry, peptide sequencing, bioinformatic protein identification, and statistical analysis. **Results:** Pooled CFS and PGI samples shared 20 proteins that were not detectable in the pooled control sample (cohort 1 CFS-related proteome). Multilogistic regression analysis (GLM) of cohort 2 detected 10 proteins that were shared by CFS individuals and the cohort 1 CFS-related proteome, but were not detected in control samples. Detection of ≈ 1 of a select set of 5 CFS-related proteins predicted CFS status with 80% concordance (logistic model). The proteins were α -1-macroglobulin, amyloid precursor-like protein 1, keratin 16, orosomucoid 2 and pigment epithelium-derived factor. Overall, 62 of 115 proteins were newly described. **Conclusion:** This pilot study detected an identical set of central nervous system, innate immune and amyloidogenic proteins in cerebrospinal fluids from two independent cohorts of subjects with overlapping CFS, PGI and fibromyalgia. Although syndrome names and definitions were different, the proteome and presumed pathological mechanism(s) may be shared. © 2005 Baraniuk et al., licensee BioMed Central Ltd.

Vladutiu G.D., Natelson B.H.

Association of medically unexplained fatigue with ACE insertion/deletion polymorphism in Gulf War veterans

2004 Muscle and Nerve 30 (1); 38 - 43

<http://www.scopus.com/inward/record.url?eid=2-s2.0-3042731743&partnerID=40>

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Genes associated with muscle metabolism and physical endurance were evaluated for variants that may contribute to the etiology of medically unexplained severe and chronic fatigue. Subjects included 49 Gulf War veterans and 61 nonveterans with chronic fatigue syndrome (CFS) or idiopathic chronic fatigue (ICF) and 30 veterans and 45 nonveterans who served as healthy controls. Increased risk for CFS/ICF was associated with alterations of the insertion/deletion (I/D) polymorphism in the angiotensin-converting enzyme gene within the Gulf War veteran sample only. The I allele frequency was decreased in affected versus unaffected veterans (0.15 versus 0.48; odds ratio [OR], 5.08; 95% confidence interval [CI], 1.97-13.35; $P < 0.0001$). Correspondingly, the II genotype was decreased fourfold in affected veterans (0.08 versus 0.35; OR = 5.87; 95% CI: 1.21-28.36; $P = 0.02$), and the DD genotype was increased twofold (0.78 versus 0.39; OR, 5.4; 95% CI, 1.6-18.4; $P = 0.007$). Veterans with the DD genotype were eight times more likely to develop CFS/ICF than were those with the II genotype (OR, 8.30; 95% CI, 1.50-56.09; $P = 0.009$).

Steinau M., Unger E.R., Vernon S.D., Jones J.F., Rajeevan M.S.
Differential-display PCR of peripheral blood for biomarker discovery in chronic fatigue syndrome

2004 Journal of Molecular Medicine 82 (11); 750 – 755

<http://www.scopus.com/inward/record.url?eid=2-s2.0-11144311220&partnerID=40>

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We used differential-display PCR of peripheral blood mononuclear cells (PBMCs) to search for candidate biomarkers for chronic fatigue syndrome (CFS). PBMCs were collected from a subject with CFS and an age-and sex-matched control before and 24 h after exercise. RNA expression profiles were generated using 46 primer combinations, and the similarity between the individuals was striking. Differentially expressed bands were excised, reamplified, and sequenced, yielding 95 nonredundant sequences, of which 50 matched to known gene transcripts, 38 matched to genes with unknown functions, and 7 had no similarity to any database entry. Most (86%) of the differences between the two subjects were present at baseline. Differential expression of ten genes was verified by real-time reverse-transcription PCR: five (cystatin F, MHC class II, platelet factor 4, fetal brain expressed sequence tag, and perforin) were downregulated, and the remaining five genes (cathepsin B, DNA polymerase β , novel EST PBMC191MSt, heparanase precursor, and ORF2/L1 element) were upregulated in the subject with CFS. Many of these genes have known functions in defense and immunity, thus supporting prior suggestions of immune dysregulation in the pathogenesis of CFS. Differential-display PCR is a powerful tool for identification of candidate biomarkers. Investigation of these markers in samples from well-designed epidemiological studies of CFS will be required to determine the validity of these candidate biomarkers. The real-time reverse-transcription PCR assays that we developed for assay of these biomarkers will facilitate high-throughput testing of these additional samples. © Springer-Verlag 2004.

Lee E., Cho S., Kim K., Park T.

An integrated approach to infer causal associations among gene expression, genotype variation, and disease

Genomics

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650252264&partnerID=40>

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Gene expression data and genotype variation data are now capable of providing genome-wide patterns across many different clinical conditions. However, the separate analysis of these data has limitations in elucidating the complex network of gene interactions underlying complex traits, such as common human diseases. More information about the identity of key driver genes of common diseases comes from integrating these two heterogeneous types of data. We developed a two-step procedure to characterize complex diseases by integrating genotype variation data and gene expression data. The first step elucidates the causal relationship among genetic variation, gene expression level, and disease. Based on the causal relationship determined at the first step, the second step identifies significant gene expression traits whose effects on disease status or whose responses to disease status are modified by the specific genotype variation. For the selected significant genes, a pathway enrichment analysis can be performed to identify the genetic mechanism of a complex disease. The proposed two-step procedure was shown to be an effective method for integrating three different levels of data, i.e., genotype variation, gene expression and disease status. By applying the proposed procedure to a chronic fatigue syndrome (CFS) dataset, we identified a list of potential causal genes for CFS, and found an evidence for difference in genetic mechanisms of the etiology between CFS without 'a major depressive disorder with melancholic features' (CFS) and CFS

with 'a major depressive disorder with melancholic features' (CFS-MDD/m). Especially, the SNPs within NR3C1 gene were shown to differently influence the susceptibility of developing CFS and CFS-MDD/m through integrative action with gene expression levels. © 2009 Elsevier Inc. All rights reserved.

Imaging

Puri B.K., Tsaluchidu S., Treasaden I.H.

Serial structural MRI analysis and proton and PMR spectroscopy in the investigation of cerebral fatty acids in major depressive disorder, huntington's disease, myalgic encephalomyelitis and in forensic schizophrenic patients

2009 World Review of Nutrition and Dietetics 99 (31); 45

<http://www.scopus.com/inward/record.url?eid=2-s2.0-62449116248&partnerID=40>

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[No abstract available]

Caseras X., Mataix-Cols D., Rimes K.A., Giampietro V., Brammer M., Zelaya F., Chalder T., Godfrey E.
The neural correlates of fatigue: An exploratory imaginal fatigue provocation study in chronic fatigue syndrome

2008 Psychological Medicine 38 (7); 941 - 951

<http://www.scopus.com/inward/record.url?eid=2-s2.0-44449155842&partnerID=40>

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Background. Fatigue is the central symptom in chronic fatigue syndrome (CFS) and yet very little is known about its neural correlates. The aim of this study was to explore the functional brain response, using functional magnetic resonance imaging (fMRI), to the imaginal experience of fatigue in CFS patients and controls. Method. We compared the blood oxygen level dependent (BOLD) responses of 12 CFS patients and 11 healthy controls to a novel fatigue provocation procedure designed to mimic real-life situations. A non-fatiguing anxiety-provoking condition was also included to control for the non-specific effects of negative affect. Results. During the provocation of fatigue, CFS patients reported feelings of both fatigue and anxiety and, compared to controls, they showed increased activation in the occipito-parietal cortex, posterior cingulate gyrus and parahippocampal gyrus, and decreased activation in dorsolateral and dorsomedial prefrontal cortices. The reverse pattern of findings was observed during the anxiety-provoking scenarios. Conclusions. The results may suggest that, in CFS patients, the provocation of fatigue is associated with exaggerated emotional responses that patients may have difficulty suppressing. These findings are discussed in relation to the cognitive-behavioural model of CFS. Copyright © 2008 Cambridge University Press.

Sherlin L., Budzynski T., Kogan Budzynski H., Congedo M., Fischer M.E., Buchwald D.

Low-resolution electromagnetic brain tomography (LORETA) of monozygotic twins discordant for chronic fatigue syndrome

2007 NeuroImage 34 (4); 1438 - 1442

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33846574234&partnerID=40>

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Background: Previous work using quantified EEG has suggested that brain activity in individuals with chronic fatigue syndrome (CFS) and normal persons differs. Our objective was to investigate if specific frequency band-pass regions and spatial locations are associated with CFS using low-resolution electromagnetic brain tomography (LORETA). Methods: We conducted a co-twin control study of 17 pairs of monozygotic twins where 1 twin met criteria for CFS and the co-twin was healthy. Twins underwent an extensive battery of tests including a structured psychiatric interview and a quantified EEG. Eyes closed EEG frequency-domain analysis was computed and the entire brain volume was compared of the CFS and healthy twins using a multiple comparison procedure. Results: Compared with their healthy co-twins, twins with CFS differed in current source density. The CFS twins had higher delta in the left uncus and parahippocampal gyrus and higher theta in the cingulate gyrus and right superior frontal gyrus. Conclusions: These findings suggest that neurophysiological activity in specific areas of the brain may differentiate individuals with CFS from those in good health. The study corroborates that slowing of the deeper structures of the limbic system is associated with affect. It also supports the neurobiological model that the right forebrain is associated with sympathetic activity and the left forebrain with the effective management of energy. These preliminary findings await replication. © 2006 Elsevier Inc. All rights reserved.

Morgan R.M., Parry A.M.M., Arida R.M., Matthews P.M., Davies B., Castell L.M.

Effects of elevated plasma tryptophan on brain activation associated with the Stroop task

2007 Psychopharmacology 190 (3); 383 - 389

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33846514685&partnerID=40>

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Rationale: Central fatigue, such as that found in chronic fatigue syndrome, is a state in which cognition and action require increasing effort and performance is impaired without evidence for reduced peripheral motor responsiveness. Previous studies identified functional changes in subcortical regions in patients who experience central fatigue but did not address neural correlates of the subjective experience of fatigue. Objectives: This study investigated responses to acute tryptophan feeding (after administration of 30 mg/kg body mass) using functional magnetic resonance imaging to investigate neural correlates of central fatigue during a cognitively demanding exercise, the counting Stroop task. Materials and methods: In a double-blind, cross-over study, eight subjects ingested L-tryptophan (Trp) or placebo (Plac) on two separate test days. Neutral (N) and interference (I) Stroop tasks were carried out. Results: Plasma-free tryptophan (p[FT]) increased tenfold after L-Trp administration ($P < 0.01$). Although reaction times were longer after Trp (mean \pm SD, Plac-Neut 669 \pm 163 ms, I 715 \pm 174 ms, $P < 0.01$; Trp-Neut 712 \pm 193 ms, I 761 \pm 198 ms, $P < 0.05$), the Stroop effect was not significantly different between Plac and Trp. L-Trp administration was associated with relatively decreased activation in regions, including the left postcentral, angular, inferior frontal, and the lateral orbital gyri and the inferior frontal sulcus relative to Plac. Relatively increased activation was found after Trp in the left precuneus and in the posterior cingulate gyrus. Conclusions: Thus, Trp administration before the Stroop task caused distributed functional changes in primary sensory and in multimodal neocortex, including changes in a brain region, the activity of which has been shown previously to vary with conscious awareness (precuneus). Previous reports suggest that primary mechanisms of central fatigue may be predominantly subcortical. The present results demonstrate that neocortical activity changes are also found. Whether this activity contributes to the primary mechanisms underlying central fatigue or not, the neocortical activity changes may provide an index of the conscious experience. © 2006 Springer-Verlag.

Cook D.B., O'Connor P.J., Lange G., Steffener J.

Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-34247244642&partnerID=40>

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The neural mechanisms underlying feelings of fatigue are poorly understood. The primary purpose of the study was to use functional magnetic resonance imaging (fMRI) to determine the association between feelings of mental fatigue and blood oxygen level dependent (BOLD) brain responses during a mentally fatiguing cognitive task. Healthy, non-fatigued controls and chronic fatigue syndrome (CFS) patients were included to determine the influence of chronic levels of fatigue on brain responses. We hypothesized that mental fatigue would be significantly related to brain activity during a fatiguing cognitive task but not during either a non-fatiguing motor (finger tapping) or cognitive (auditory monitoring) task. Patients (n = 9) and controls (n = 11) completed a finger tapping task, a simple auditory monitoring task and a challenging working memory task, designed to induce mental fatigue, while undergoing fMRI. Fatigue was measured prior to scanning and following each task during fMRI data collection. Results showed that mental fatigue was significantly related to brain activity during the fatiguing cognitive task but not the finger tapping or simple auditory monitoring tasks. Significant ($p < 0.005$) positive relationships were found for cerebellar, temporal, cingulate and frontal regions. A significant ($p = 0.001$) negative relationship was found for the left posterior parietal cortex. CFS participants did not differ from controls for either finger tapping or auditory monitoring tasks, but exhibited significantly greater activity in several cortical and subcortical regions during the fatiguing cognitive task. Our results suggest an association between subjective feelings of mental fatigue and brain responses during fatiguing cognition. © 2007 Elsevier Inc. All rights reserved.

Tanaka M., Sadato N., Okada T., Mizuno K., Sasabe T., Tanabe H.C., Saito D.N., Onoe H., Kuratsune H., Wanatabe Y.

Reduced responsiveness is an essential feature of chronic fatigue syndrome: A fMRI study

2006 BMC Neurology 6

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33644918283&partnerID=40>

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Background: Although the neural mechanism of chronic fatigue syndrome has been investigated by a number of researchers, it remains poorly understood. Methods: Using functional magnetic resonance imaging, we studied brain responsiveness in 6 male chronic fatigue syndrome patients and in 7 age-matched male healthy volunteers. Responsiveness of auditory cortices to transient, short-lived, noise reduction was measured while subjects performed a fatigue-inducing continual visual search task.

Results: Responsiveness of the task-dependent brain regions was decreased after the fatigue-inducing task in the normal and chronic fatigue syndrome subjects and the decrement of the responsiveness was equivalent between the 2 groups. In contrast, during the fatigue-inducing period, although responsiveness of auditory cortices remained constant in the normal subjects, it was attenuated in the chronic fatigue syndrome patients. In addition, the rate of this attenuation was positively correlated with the subjective sensation of fatigue as measured using a fatigue visual analogue scale, immediately before the magnetic resonance imaging session. Conclusion: Chronic fatigue syndrome may be characterised by attenuation of the responsiveness to stimuli not directly related to the fatigue-inducing task. © 2006 Tanaka et al; licensee BioMed Central Ltd.

Spence S.A.

All in the mind? The neural correlates of unexplained physical symptoms

2006 *Advances in Psychiatric Treatment* 12 (5); 349 – 358

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Physical symptoms with no medical explanation are commonly experienced by healthy people and those attending clinics. Psychiatrists see such patients in liaison settings and clinics for those with psychotic and affective disorders. The pathophysiology remains obscure; physical investigations are usually performed to exclude pathology rather than elucidate dysfunction. However, modern neuroimaging has allowed the study of nervous system structure and function. Although there are few diagnostically specific findings, patterns of association have emerged: where action is impeded (certain forms of conversion disorder and chronic fatigue syndrome) frontal systems of the brain are often implicated; when subjective awareness of the body is disturbed (passivity phenomena and anorexia nervosa) temporoparietal cortices appear to be dysfunctional. The caudate nuclei (components of the frontal executive circuit) are implicated in a variety of syndromes (including body dysmorphic disorder, somatisation and chronic fatigue). The brain may be viewed as a cognitive neurobiological entity, crucially oriented towards action (for survival). Psychiatric syndromes that have an impact on bodily awareness signal dysfunction within systems representing that body and its performance in time and space.

Caseras X., Mataix-Cols D., Giampietro V., Rimes K.A., Brammer M., Zelaya F., Chalder T., Godfrey E.L.

Probing the working memory system in chronic fatigue syndrome: A functional magnetic resonance imaging study using the n-back task

2006 *Psychosomatic Medicine* 68 (6); 947 - 955

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OBJECTIVE: Up to 90% of patients with chronic fatigue syndrome (CFS) report substantial cognitive difficulties. However, objective evidence supporting these claims is inconsistent. The present functional magnetic resonance imaging study examined the neural correlates of working memory in patients with CFS compared with controls. **METHODS:** Seventeen patients with CFS and 12 healthy control subjects were scanned while performing a parametric version of the n-back task (0-, 1-, 2-, and 3-back). **RESULTS:** Both groups performed comparably well and activated the verbal working memory network during all task levels. However, during the 1-back condition, patients with CFS showed greater activation than control subjects in medial prefrontal regions, including the anterior cingulate gyrus. Conversely, on the more challenging conditions, patients with CFS demonstrated

reduced activation in dorsolateral prefrontal and parietal cortices. Furthermore, on the 2- and 3-back conditions, patients but not control subjects significantly activated a large cluster in the right inferior/medial temporal cortex. Trend analyses of task load demonstrated statistically significant differences in brain activation between the two groups as the demands of the task increased. CONCLUSIONS: These results suggest that patients with CFS show both quantitative and qualitative differences in activation of the working memory network compared with healthy control subjects. It remains to be determined whether these findings stay stable after successful treatment. Copyright © 2006 by American Psychosomatic Society.

Lange G., Steffener J., Cook D.B., Bly B.M., Christodoulou C., Liu W.-C., DeLuca J., Natelson B.H.
Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: A BOLD fMRI study of verbal working memory

2005 NeuroImage 26 (2); 513 - 524

<http://www.scopus.com/inward/record.url?eid=2-s2.0-19344368494&partnerID=40>

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Individuals with Chronic Fatigue Syndrome (CFS) often have difficulties with complex auditory information processing. In a series of two Blood Oxygen Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) studies, we compared BOLD signal changes between Controls and individuals with CFS who had documented difficulties in complex auditory information processing (Study 1) and those who did not (Study 2) in response to performance on a simple auditory monitoring and a complex auditory information processing task (mPASAT). We hypothesized that under conditions of cognitive challenge: (1) individuals with CFS who have auditory information processing difficulties will utilize frontal and parietal brain regions to a greater extent than Controls and (2) these differences will be maintained even when objective difficulties in this domain are controlled for. Using blocked design fMRI paradigms in both studies, we first presented the auditory monitoring task followed by the mPASAT. Within and between regions of interest (ROI), group analyses were performed for both studies with statistical parametric mapping (SPM99). Findings showed that individuals with CFS are able to process challenging auditory information as accurately as Controls but utilize more extensive regions of the network associated with the verbal WM system. Individuals with CFS appear to have to exert greater effort to process auditory information as effectively as demographically similar healthy adults. Our findings provide objective evidence for the subjective experience of cognitive difficulties in individuals with CFS. © 2005 Elsevier Inc. All rights reserved.

Cleare A.J., Messa C., Rabiner E.A., Grasby P.M.
Brain 5-HT_{1A} receptor binding in chronic fatigue syndrome measured using positron emission tomography and [¹¹C]WAY-100635

2005 Biological Psychiatry 57 (3); 239 - 246

<http://www.scopus.com/inward/record.url?eid=2-s2.0-13244291518&partnerID=40>

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Research from neuroendocrine challenge and other indirect studies has suggested increased central 5-HT function in chronic fatigue syndrome (CFS) and increased 5-HT_{1A} receptor sensitivity. We assessed brain 5-HT_{1A} receptor binding potential directly using the specific radioligand [¹¹C]WAY-100635 and positron emission tomography (PET). We selected 10 patients from a tertiary referral clinic who fulfilled the CDC consensus criteria for CFS. To assemble a homogenous group and avoid confounding effects, we enrolled only subjects who were completely medication-free and did not have current comorbid psychiatric illness. We also scanned 10 healthy control subjects. There was a widespread reduction in 5-HT_{1A} receptor binding potential in CFS relative to control subjects. This was particularly marked in the hippocampus bilaterally, where a 23% reduction was observed. There is evidence of decreased 5-HT_{1A} receptor number or affinity in CFS. This may be a primary feature of CFS, related to the underlying pathophysiology, or a finding secondary to other processes, such as previous depression, other biological changes or the behavioral consequences of CFS.

Cox I.J., Puri B.K.

In vivo MR spectroscopy in diagnosis and research of neuropsychiatric disorders

2004 Prostaglandins Leukotrienes and Essential Fatty Acids 70 (4); 357 – 360

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Magnetic resonance spectroscopy is one of the most important tools for quantitative analysis of chemical composition and structure, and this non-invasive technique is now being applied in vivo to study biochemical processes in those neuropsychiatric disorders that are part of the phospholipid spectrum. Interpretation of a clinical magnetic resonance spectrum can provide information about membrane phospholipid turnover, cellular energetics, neuronal function, selected neurotransmitter activity and intracellular pH. Cerebral proton and phosphorus magnetic resonance spectroscopy findings are summarized in relation to schizophrenia, dyslexia and chronic fatigue syndrome. © 2004 Elsevier Ltd. All rights reserved.

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In vivo magnetic resonance spectroscopy in chronic fatigue syndrome

2004 Prostaglandins Leukotrienes and Essential Fatty Acids 71 (3); 181 – 183

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The pathogenic mechanisms of chronic fatigue syndrome (CFS) are not clearly known. Fatigue, poor short-term memory and muscle pain are the most disabling symptoms in CFS. Research data on magnetic resonance spectroscopy (MRS) of muscles and brain in CFS patients suggest a cellular metabolic abnormality in some cases. ³¹P MRS of skeletal muscles in a subset of patients indicate early intracellular acidosis in the exercising muscles. ¹H MRS of the regional brain areas in CFS have shown increased peaks of choline derived from the cell membrane phospholipids. Cell membrane oxidative stress may offer a common explanation for the observed MRS changes in the muscles and brain of CFS patients and this may have important therapeutic implications. As a research tool, MRS may be used as an objective outcome measure in the intervention studies. In addition, regional brain ¹H MRS has the potential for wider use to substantiate a clinical diagnosis of CFS from other disorders of unexplained chronic fatigue. © 2004 Elsevier Ltd. All rights reserved.

Immune dysregulation & infection

Vij G., Gupta A., Chopra K.

Modulation of antigen-induced chronic fatigue in mouse model of water immersion stress by naringin, a polyphenolic antioxidant

2009 Fundamental and Clinical Pharmacology 23 (3); 331 – 337

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It is believed that physical stress, infection and oxidative stress are involved in the development of chronic fatigue syndrome. There is little evidence stating the beneficial role of nutritional supplements in chronic fatigue syndrome. Based on this, this study was designed to evaluate the effect of naringin, a natural polyphenol, in a mouse model of immunologically-induced fatigue, wherein purified lipopolysaccharide (LPS) as well as *Brucella abortus* (BA) antigen was used as immunogens. The assessment of chronic fatigue syndrome was based on chronic water-immersion stress test for 10 mins as well as measurement of hyperalgesia for 19 days. Immobility time and tail withdrawal latency as well as oxidative stress were taken as the markers of fatigue. Mice challenged with LPS or BA for 19 days showed significant increase in the immobility time, hyperalgesia and oxidative stress on 19th day. Serum tumor necrosis factor-alpha (TNF- α) levels markedly increased with LPS or BA challenge. Concurrent treatment with naringin resulted in the significant decrease in the immobility time as well as hyperalgesia. There was significant attenuation of oxidative stress as well as in TNF- α levels. Present findings strongly suggest the role of oxidative stress and immunological activation in the pathophysiology of chronic fatigue syndrome, and treatment with naringin can be a valuable option in chronic fatigue syndrome. © 2009 Soci t  Fran saise de Pharmacologie et de Th rapeutique.

Sorensen B., Jones J.F., Vernon S.D., Rajeevan M.S.

Transcriptional control of complement activation in an exercise model of chronic fatigue syndrome

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Complement activation resulting in significant increases of C4a split product may be a marker of postexertional malaise in individuals with chronic fatigue syndrome (CFS). This study focused on identification of the transcriptional control that may contribute to the increased C4a in CFS subjects after exercise. We used quantitative reverse-transcription polymerase chain reaction to evaluate differential expression of genes in the classical and lectin pathways in peripheral blood mononuclear cells (PBMCs). Calibrated expression values were normalized to the internal reference gene peptidylpropyl isomerase B (PPIB), the external reference gene ribulose-1,5-bisphosphate carboxylase/oxygenase large subunit (rbcL), or the geometric mean (GM) of the genes ribosomal protein, large, PO (RPLPO) and phosphoglycerate kinase 1 (PGK1). All nine genes tested, except mannose-binding lectin 2 (MBL2), were expressed in PBMCs. At 1 hour postexercise, C4, mannan-binding lectin serine protease 2 (MASP2) and ficolin 1 (FCN1) transcripts were detected at higher levels (≥ 2 -fold) in at least 50% (4 of 8) of CFS subjects and were detected in 88% (7 of 8) CFS subjects when subjects with overexpression of either C4 or MASP2 were combined. Only an increase in the MASP2 transcript was statistically significant (PPIB, $P = 0.001$; GM, $P = 0.047$; rbcL, $P = 0.045$). This result may be due to the significant but transient downregulation of MASP2 in control subjects (PPIB, $P = 0.023$; rbcL, $P = 0.027$). By 6 hours postexercise, MASP2 expression was similar in both groups. In conclusion, lectin pathway responded to exercise differentially in CFS than in control

subjects. MASP2 downregulation may act as an antiinflammatory acute-phase response in healthy subjects, whereas its elevated level may account for increased C4a and inflammation-mediated postexertional malaise in CFS subjects. © 2009 The Feinstein Institute for Medical Research.

Raison C.L., Lin J.-M.S., Reeves W.C.

Association of peripheral inflammatory markers with chronic fatigue in a population-based sample

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-61349116729&partnerID=40>

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Alterations in the innate immune response may contribute to the pathogenesis of chronic fatigue syndrome (CFS). However, studies have been limited by small sample sizes, use of patients from tertiary care settings, inappropriate selection of controls, and failure to control for confounding demographic, medical and behavioral factors independently associated with immune activity. It is also not known whether specific symptoms account for observed associations between CFS and the innate immune response. To address these limitations, the current study examined plasma concentrations of high-sensitivity c-reactive protein (hs-CRP), white blood cell count (WBC) and a combined inflammation factor in a large population-based sample. Log-transformed mean plasma concentrations of hs-CRP were increased in subjects with CFS (n = 102) and in subjects with unwellness symptoms that did not meet diagnostic criteria for CFS (defined as "insufficient fatigue" [ISF]) (n = 240) when compared to subjects who were well (n = 115). Log transformed WBC was increased in ISF and was increased at a trend level in CFS. The combined inflammation factor was increased in both CFS and ISF. Subjects with CFS and ISF did not differ on any of the inflammation measures. In the entire subject population, the physical component summary score (PCS), but not the mental component summary score (MCS), from the Medical Outcomes Study Short Form-36 (SF-36) was negatively associated with each of the inflammation measures. Depressive symptoms were also associated with increased log hs-CRP. After adjustment for age, sex, race, location of residence, BMI, depressive status and immune-modulating medications, subjects classified as ISF continued to demonstrate increased log hs-CRP, WBC and elevations on the inflammation factor when compared to well controls; however, associations between CFS and log hs-CRP and the inflammation factor were no longer statistically significant. After adjustment, PCS score also remained independently associated with each of the inflammation measures. These findings support a role for innate immune activation in unexplained fatigue and unwellness, but do not suggest that immune activation is specific to CFS. © 2008 Elsevier Inc.

Kuo Y.-H., Tsai W.-J., Loke S.-H., Wu T.-S., Chiou W.-F.

Astragalus membranaceus flavonoids (AMF) ameliorate chronic fatigue syndrome induced by food intake restriction plus forced swimming

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-59849128091&partnerID=40>

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Aim of the study: Alteration of immune function may be associated with chronic fatigue syndrome (CFS) and this study reveals the immunoregulatory effect of *Astragalus membranaceus* flavonoids (AMF). Materials and methods: CF rats were induced by food intake restriction plus forced swimming for 6 weeks. Results: An atrophied spleen associated with a significantly decreased spleen/body weight ratio and a reduced spleen cells proliferation was found in CF rats when compared with home cage controls. AMF given orally at 20, 50 and 100 mg/kg body weight once a day consecutively for 6 weeks could recover the reduced cell proliferation. A switch to Th1-dominated immune regulation was observed in CF rats as the cultured splenocytes produced more interleukin-2 (IL-2) but less IL-4 when

compared with controls. Supplementation with AMF could significantly counteract the aberrant cytokine production and rats received AMF exhibited higher endurance capacity to swim when compared with those without AMF administration. Checking the spectrum signals confirmed that the three major isoflavones contained in AMF were ononin, formononetin, and demethylhomopterocarpin. Conclusion: Alterations of immune function may be associated with CFS and the tonic effects of AMF against CF may be attributable to balance the abnormal cytokine level by isoflavones. © 2008 Elsevier Ireland Ltd. All rights reserved.

Hokama Y., Campora C.E., Hara C., Kuribayashi T., Le Huynh D., Yabusaki K.
Anticardiolipin antibodies in the sera of patients with diagnosed chronic fatigue syndrome

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Examination of anticardiolipin antibodies (ACAs) in the sera of patients clinically diagnosed with chronic fatigue syndrome (CFS) using an enzyme-linked immunoassay procedure demonstrated the presence of immunoglobulin M isotypes in 95% of CFS serum samples tested. The presence of immunoglobulin G and immunoglobulin A isotypes were also detected in a subset of the samples. Future studies will focus on elucidating whether alterations to mitochondrial inner membranes and/or metabolic functions play a possible role in the expression of ACAs. © 2009 Wiley-Liss, Inc.

Gupta A., Vij G., Sharma S., Tirkey N., Rishi P., Chopra K.
Curcumin, a polyphenolic antioxidant, attenuates chronic fatigue syndrome in murine water immersion stress model

2009 Immunobiology 214 (1); 33 - 39

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Chronic fatigue syndrome, infection and oxidative stress are interrelated in epidemiological case studies. However, data demonstrating scientific validation of epidemiological claims regarding effectiveness of nutritional supplements for chronic fatigue syndrome are lacking. This study is designed to evaluate the effect of natural polyphenol, curcumin, in a mouse model of immunologically induced fatigue, where purified lipopolysaccharide (LPS) and *Brucella abortus* (BA) antigens were used as immunogens. The assessment of chronic fatigue syndrome was based on chronic water-immersion stress test for 10 min daily for 19 days and the immobility time was taken as the marker of fatigue. Mice challenged with LPS or BA for 19 days showed significant increase in the immobility time and hyperalgesia on day 19, as well as marked increase in serum tumor necrosis factor- α (TNF- α) levels. Concurrent treatment with curcumin resulted in significantly decreased immobility time as well as hyperalgesia. There was significant attenuation of oxidative stress as well as TNF- α levels. These findings strongly suggest that during immunological activation, there is significant increase in oxidative stress and curcumin can be a valuable option in the treatment of chronic fatigue syndrome. © 2008 Elsevier GmbH. All rights reserved.

Fluge O., Mella O.

Clinical impact of B-cell depletion with the anti-CD20 antibody rituximab in chronic fatigue syndrome: A preliminary case series

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-67651160583&partnerID=40>

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Background: Chronic fatigue syndrome (CFS) is a disease of unknown aetiology. A patient with CFS had unexpected, marked recovery of CFS symptoms lasting for five months during and after cytotoxic chemotherapy for Hodgkin's disease. We reasoned that the transient CFS recovery was related to methotrexate treatment, which induces immunomodulation in part through B-cell depletion. Methods: In a case series, this patient and two additional CFS patients were B-cell depleted by infusion of the monoclonal anti-CD20 antibody rituximab. Results: All three had improvement of all CFS symptoms. Patients 1 and 2 had major amelioration from 6 weeks after intervention, patient 3 slight improvement from the same time, but then improved markedly from 26 weeks after intervention. The symptomatic effect lasted until weeks 16, 18 and 44, respectively. At relapse, all were retreated with a single (patient 1) or double rituximab infusion (patients 2 and 3). Again, all three had marked symptom improvement, mimicking their first response. After new symptom recurrence, patients 1 and 2 were given weekly oral methotrexate, patient 1 having effect also from this agent. Patients 1 and 2 were again treated for a third rituximab infusion after new relapse, again with a marked clinical benefit. No unexpected toxicity was seen. Conclusion: These observations suggest that B-lymphocytes are involved in CFS pathogenesis for a subset of patients. Benefit for all CFS symptoms, the delayed symptom relief following B-cell depletion, the kinetics of relapses, and the effect also from methotrexate treatment, provide suggestive evidence that B-cells play a significant role in the ongoing clinical features, and that CFS may be amenable to therapeutic interventions aimed at modifying B-cell number and function. More systematic investigations of this therapeutic strategy, and of its biological basis, are now needed. © 2009 Fluge and Mella; licensee BioMed Central Ltd.

Sullivan A., Nord C.E., Evengard B.

Effect of supplement with lactic-acid producing bacteria on fatigue and physical activity in patients with chronic fatigue syndrome

2009 Nutrition Journal 8 (1)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-60849105671&partnerID=40>

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Disturbances in intestinal microbial ecology and in the immune system of the host have been implicated as a part of the pathogenesis in chronic fatigue syndrome. Probiotic lactic acid producing bacteria have been shown to prevent and alleviate gastrointestinal disturbances and to normalize the cytokine profile which might be of an advantage for patients suffering from chronic fatigue syndrome. The aim of the study was to evaluate the effect of *Lactobacillus paracasei* ssp. *paracasei* F19, *Lactobacillus acidophilus* NCFB 1748 and *Bifidobacterium lactis* Bb12 on fatigue and physical activity in CFS patients. Fifteen patients fulfilling the criteria set by international researchers in the field at the US Centre for Disease Control and Prevention in 1994 for chronic fatigue syndrome, were included in the study. The patients had high fatigue severity scores and high disability scores. During the first two weeks baseline observations without treatment were assessed, succeeded by four weeks of intake of a probiotic product and a four-week follow-up period. The fatigue, health and physical activity was assessed by the use of the Visual Analogue Scales and the SF-12 Health Survey. Faecal samples were collected and the normal microflora was analysed. Neurocognitive functions improved during the study period while there were no significant changes in fatigue and physical activity scores. No major changes occurred in the gastrointestinal microflora. At the end of the study 6 of 15 patients reported

that they had improved according to the assessment described. The findings in this study that improvement of health is possible to achieve should encourage further studies with interventions with probiotics in patients with CFS. © 2009 Sullivan et al; licensee BioMed Central Ltd.

Sheedy J.R., Wettenhall R.E.H., Scanlon D., Gooley P.R., Lewis D.P., McGregor N., Stapleton D.I., Butt H.L., De Meirleir K.L.

Increased D-lactic acid intestinal bacteria in patients with chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650967026&partnerID=40>

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Patients with chronic fatigue syndrome (CFS) are affected by symptoms of cognitive dysfunction and neurological impairment, the cause of which has yet to be elucidated. However, these symptoms are strikingly similar to those of patients presented with D-lactic acidosis. A significant increase of Gram positive facultative anaerobic faecal microorganisms in 108 CFS patients as compared to 177 control subjects ($p < 0.01$) is presented in this report. The viable count of D-lactic acid producing *Enterococcus* and *Streptococcus* spp. in the faecal samples from the CFS group (3.5×10^7 cfu/L and 9.8×10^7 cfu/L respectively) were significantly higher than those for the control group (5.0×10^6 cfu/L and 8.9×10^4 cfu/L respectively). Analysis of exo-metabolic profiles of *Enterococcus faecalis* and *Streptococcus sanguinis*, representatives of *Enterococcus* and *Streptococcus* spp. respectively, by NMR and HPLC showed that these organisms produced significantly more lactic acid ($p < 0.01$) from ^{13}C -labeled glucose, than the Gram negative *Escherichia coli*. Further, both *E. faecalis* and *S. sanguinis* secrete more D-lactic acid than *E. coli*. This study suggests a probable link between intestinal colonization of Gram positive facultative anaerobic D-lactic acid bacteria and symptom expressions in a subgroup of patients with CFS. Given the fact that this might explain not only neurocognitive dysfunction in CFS patients but also mitochondrial dysfunction, these findings may have important clinical implications.

Magnus P., Brubakk O., Nyland H., Wold B.H., Gjessing H.K., Brandt I., Eidem T., Nokleby H., Stene-Larsen G.

Vaccination as teenagers against meningococcal disease and the risk of the chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-56949097011&partnerID=40>

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The etiology of chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) is unknown. In Norway, a vaccine against *Neisseria meningitidis* group B was administered to teenagers in 1988-1989 in a protection trial. In order to estimate the relative risk of CFS/ME according to vaccine history, we conducted a case-control study in 2007, with 201 cases diagnosed at one of two hospitals and 389 controls. The adjusted odds ratio for CFS/ME was 1.06 (95% CI: 0.67-1.66) for subjects who received the active vaccine contrasted to subjects who did not. Using this design, no statistically significant association between vaccination against meningococcal disease in teenagers and occurrence of CFS/ME could be observed. © 2008 Elsevier Ltd. All rights reserved.

Katz B.Z., Shiraishi Y., Mears C.J., Binns H.J., Taylor R.
Chronic fatigue syndrome after infectious mononucleosis in adolescents

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-67649584084&partnerID=40>

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OBJECTIVE: The goal was to characterize prospectively the course and outcome of chronic fatigue syndrome in adolescents during a 2-year period after infectious mononucleosis. **METHODS:** A total of 301 adolescents (12-18 years of age) with infectious mononucleosis were identified and screened for nonrecovery 6 months after infectious mononucleosis by using a telephone screening interview. Nonrecovered adolescents underwent a medical evaluation, with follow-up screening 12 and 24 months after infectious mononucleosis. After blind review, final diagnoses of chronic fatigue syndrome at 6, 12, and 24 months were made by using established pediatric criteria. **RESULTS:** Six, 12, and 24 months after infectious mononucleosis, 13%, 7%, and 4% of adolescents, respectively, met the criteria for chronic fatigue syndrome. Most individuals recovered with time; only 2 adolescents with chronic fatigue syndrome at 24 months seemed to have recovered or had an explanation for chronic fatigue at 12 months but then were reclassified as having chronic fatigue syndrome at 24 months. All 13 adolescents with chronic fatigue syndrome 24 months after infectious mononucleosis were female and, on average, they reported greater fatigue severity at 12 months. Reported use of steroid therapy during the acute phase of infectious mononucleosis did not increase the risk of developing chronic fatigue syndrome. **CONCLUSIONS:** Infectious mononucleosis may be a risk factor for chronic fatigue syndrome in adolescents. Female gender and greater fatigue severity, but not reported steroid use during the acute illness, were associated with the development of chronic fatigue syndrome in adolescents. Additional research is needed to determine other predictors of persistent fatigue after infectious mononucleosis. Copyright © 2009 by the American Academy of Pediatrics.

Fremont M., Metzger K., Rady H., Hulstaert J., De Meirleir K.
Detection of herpesviruses and parvovirus B19 in gastric and intestinal mucosa of chronic fatigue syndrome patients

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-64549163255&partnerID=40>

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Background: Human herpesvirus-6 (HHV-6), Epstein-Barr virus and parvovirus B19 have been suggested as etiological agents of chronic fatigue syndrome but none of these viruses is consistently detected in all patients. However, active viral infections may be localized in specific tissues, and, therefore, are not easily detectable. The aim of this study was to investigate the presence of HHV-6, HHV-7, EBV and parvovirus B19 in the gastro-intestinal tract of CFS patients. **Patients and Methods:** Using real-time PCR, viral DNA loads were quantified in gastro-intestinal biopsies of 48 CFS patients and 35 controls. **Results:** High loads of HHV-7 DNA were detected in most CFS and control biopsies. EBV and HHV-6 were detected in 15-30% of all biopsies. Parvovirus B19 DNA was detected in 40% of the patients versus less than 15% of the controls. **Conclusion:** Parvovirus B19 may be involved in the pathogenesis of CFS, at least for a subset of patients. The gastro-intestinal tract appears as an important reservoir of infection for several potentially pathogenic viruses.

Exley C., Swarbrick L., Gherardi R.K., Authier F.-J.

A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome

2009 Medical Hypotheses 72 (2); 135 - 139

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Macrophagic myofasciitis and chronic fatigue syndrome are severely disabling conditions which may be caused by adverse reactions to aluminium-containing adjuvants in vaccines. While a little is known of disease aetiology both conditions are characterised by an aberrant immune response, have a number of prominent symptoms in common and are coincident in many individuals. Herein, we have described a case of vaccine-associated chronic fatigue syndrome and macrophagic myofasciitis in an individual demonstrating aluminium overload. This is the first report linking the latter with either of these two conditions and the possibility is considered that the coincident aluminium overload contributed significantly to the severity of these conditions in this individual. This case has highlighted potential dangers associated with aluminium-containing adjuvants and we have elucidated a possible mechanism whereby vaccination involving aluminium-containing adjuvants could trigger the cascade of immunological events which are associated with autoimmune conditions including chronic fatigue syndrome and macrophagic myofasciitis.   2008 Elsevier Ltd. All rights reserved.

Thambirajah A.A., Sleight K., Stiver H.G., Chow A.W.

Differential heat shock protein responses to strenuous standardized exercise in chronic fatigue syndrome patients and matched healthy controls

2008 Clinical and Investigative Medicine 31 (6)

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Purpose: Since physical exertion is known to exacerbate the symptoms of chronic fatigue syndrome (CFS) and metabolic changes and including oxidative stress can modulate heat shock protein (HSP) expression responses, we sought to determine whether HSP expression is altered in CFS patients before and after exercise. Heat shock proteins (HSPs) in peripheral blood mononuclear cells (PBMC) were examined from 6 chronic fatigue syndrome (CFS) patients and 7 controls before and after a standardized treadmill exercise. Basal hsp27 was significantly higher among CFS patients compared to controls, and decreased immediately post-exercise, remaining below basal levels even at 7 days. A similar pattern was observed for HSP60, which gradually decreased in CFS patients but increased in controls post-exercise. These findings suggest an abnormal adaptive response to oxidative stress in CFS, and raise the possibility that HSP profiling may provide a more objective biologic marker for this illness. Methods: HSP27, HSP60, HSP70 and HSP90 expression from 6 CFS patients and 7 age- and sex-matched controls were examined by western blot analysis of peripheral blood mononuclear cells immediately before, after, and at 1 day and 7 days following a standardized treadmill exercise. Results: Basal HSP27 was higher among CFS patients than in controls (0.54 ± 0.13 vs. 0.19 ± 0.06 , mean \pm SEM; $P < 0.01$). In addition, these levels in CFS patients decreased immediately post-exercise (0.25 ± 0.09 ; $P < 0.05$) and remained below basal levels at day 1 post-exercises (0.18 ± 0.05 ; $P < 0.05$). This declining expression of HSP27 during the post-exercise period among CFS patients was confirmed by one-way ANOVA analysis with repeated measures ($P < 0.05$). In contrast, HSP27 levels remained relatively constant following exercise among control subjects. Similar

patterns of declining HSP levels in CFS patients were also observed for HSP60 (0.94 ± 0.40 vs. 1.32 ± 0.46 ; $P < 0.05$), and for HSP90 (0.34 ± 0.09 vs. 0.49 ± 0.10 ; $P < 0.05$) at day 7 post-exercise compared with basal levels, respectively. In contrast, HSP60 levels in control subjects increased at day 1 (1.09 ± 0.27) and day 7 (1.24 ± 0.50) post-exercise compared to corresponding levels immediately post-exercise (0.55 ± 0.06) ($P < 0.05$, respectively). Conclusion: These preliminary findings suggest an abnormal or defective adaptive response to oxidative stress in CFS, and raise the possibility that HSP profiling may provide a more objective biologic marker for this illness. © 2008 CIM.

Wolbeek M., van Doornen L.J.P., Schedlowski M., Janssen O.E., Kavelaars A., Heijnen C.J.
Glucocorticoid sensitivity of immune cells in severely fatigued adolescent girls: A longitudinal study

2008 Psychoneuroendocrinology 33 (3); 375 - 385

<http://www.scopus.com/inward/record.url?eid=2-s2.0-39149083403&partnerID=40>

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Fatigue during adolescence is associated with somatic and psychological complaints that resemble the pattern of symptoms described for chronic fatigue syndrome (CFS). Studies in CFS and other stress-related syndromes suggested a dysfunction of the interactions between the hypothalamic-pituitary-adrenal axis (HPA-axis) and the immune system, i.e. a changed glucocorticoid (GC) receptor sensitivity of immune cells, to exist. Here we investigated whether severely fatigued girls from a healthy population have altered cortisol production and immune cell sensitivity for the synthetic GC, dexamethasone (DEX). In a longitudinal design, we examined ex vivo DEX sensitivity of monocytes and of T-cell mitogen-induced responses of severely fatigued (N=65) and non-fatigued girls (N=60). Fatigued girls reported more severe comorbid complaints than non-fatigued participants across three measurements during 1 year (T1: spring, T2: autumn, T3: spring) and had higher plasma cortisol levels throughout the study. DEX sensitivity of T-cell mitogen-induced responses showed seasonal variation with increased sensitivity in autumn compared to spring. No systematic variation of monocyte glucocorticoid receptor (GR) sensitivity was observed. Significant rank correlations of DEX sensitivity of T-cell mitogen-induced responses between the three assessments during the year suggest a stable trait of immune function. Groups did not differ in DEX sensitivity on any of the read outs. However, in a persistently fatigued subgroup, sensitivity to DEX was significantly reduced on the level of interferon (IFN)- γ production. These results show that although fatigued participants had severe (comorbid) complaints, only in the case when symptoms persisted, altered GC sensitivity of immune cells was observed. © 2007 Elsevier Ltd. All rights reserved.

Pall M.L.

Post-radiation syndrome as a NO/ONOO- cycle, chronic fatigue syndrome-like disease

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-50449083288&partnerID=40>

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Post-radiation syndrome is proposed to be chronic fatigue syndrome (CFS) or a chronic fatigue syndrome-like illness, initiated by exposure to ionizing radiation. This view is supported by the nitric oxide/peroxynitrite (NO/ONOO-) cycle mechanism, the putative etiologic mechanism for CFS and related illnesses. Ionizing radiation may initiate illness by increasing nitric oxide levels via increased activity of the transcription factor NF- κ B and consequent increased synthesis of the inducible nitric oxide synthase. Two types of components of the nitric oxide/peroxynitrite cycle have been studied in post-radiation syndrome patients and shown to be elevated. The symptoms and signs of post-radiation

syndrome and its chronicity are similar or identical to those of chronic fatigue syndrome and can be explained as being a consequence of nitric oxide/peroxynitrite cycle etiology. While the data available to test this view are limited, it provides for the first time a comprehensive explanation for post-radiation syndrome. © 2008 Elsevier Ltd. All rights reserved.

Metzger K., Fremont M., Roelant C., De Meirleir K.

Lower frequency of IL-17F sequence variant (His161Arg) in chronic fatigue syndrome patients

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Chronic fatigue syndrome (CFS) is characterized by immune dysfunctions including chronic immune activation, inflammation, and alteration of cytokine profiles. T helper 17 (Th17) cells belong to a recently identified subset of T helper cells, with crucial regulatory function in inflammatory and autoimmune processes. Th17 cells are implicated in allergic inflammation, intestinal diseases, central nervous system inflammation, disorders that may all contribute to the pathophysiology of CFS. IL-17F is one of the pro-inflammatory cytokines secreted by Th17 cells. We investigated the association between CFS and the frequency of rs763780, a C/T genetic polymorphism leading to His161Arg substitution in the IL-17F protein. The His161Arg variant (C allele) antagonizes the pro-inflammatory effects of the wild-type IL-17F. A significantly lower frequency of the C allele was observed in the CFS population, suggesting that the His161Arg variant may confer protection against the disease. These results suggest a role of Th17 cells in the pathogenesis of CFS. © 2008 Elsevier Inc. All rights reserved.

Meeus M., Nijs J., McGregor N., Meeusen R., De Schutter G., Truijen S., Fremont M., Van Hoof E., De Meirleir K.

Unravelling intracellular immune dysfunctions in chronic fatigue syndrome: Interactions between protein kinase R activity, RNase L cleavage and elastase activity, and their clinical relevance

2008 In Vivo 22 (1); 115 - 122

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This study examined possible interactions between immunological abnormalities and symptoms in CFS. Sixteen CFS patients filled in a battery of questionnaires, evaluating daily functioning, and underwent venous blood sampling, in order to analyse immunological abnormalities. Ribonuclease (RNase) L cleavage was associated with RNase L activity ($rs=0.570$; $p=0.021$), protein kinase R (PKR) ($rs=0.716$; $p=0.002$) and elastase activity ($rs=0.500$; $p=0.049$). RNase L activity was related to elastase ($rs=0.547$; $p=0.028$) and PKR activity ($rs=0.625$; $p=0.010$). RNase L activity ($rs=0.535$; $p=0.033$), elastase activity ($rs=0.585$; $p=0.017$) and RNase L cleavage ($rs=0.521$; $p=0.038$) correlated with daily functioning. This study suggests that in CFS patients an increase in elastase activity and subsequent RNase L cleavage is accompanied by increased activity of both the PKR and RNase L enzymes. RNase L and elastase activity are related to daily functioning, thus evidence supporting the clinical importance of these immune dysfunctions in CFS patients was provided.

Maes M., Mihaylova I., Kubera M., Leunis J.-C.

An IgM-mediated immune response directed against nitro-bovine serum albumin (nitro-BSA) in chronic fatigue syndrome (CFS) and major depression: Evidence that nitrosative stress is another factor underpinning the comorbidity between major depression and CFS

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-48049089358&partnerID=40>

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Background: It has been shown that chronic fatigue syndrome (CFS) and major depression (MDD) are accompanied by signs of oxidative stress and by a decreased antioxidant status. The aim of the present study was to examine whether CFS and MDD are accompanied by an IgM-mediated immune response directed against nitro-serum bovine albumin (BSA), which is a neoepitope of BSA formed by damage caused by nitrosative stress. **Aims:** Toward this end, we examined serum IgM antibodies to nitro-BSA in 13 patients with CFS, 14 subjects with partial CFS, 16 patients with MDD and 11 normal controls. **Results:** We found that the prevalence and mean values for the serum IgM levels directed against nitro-BSA were significantly greater in patients with partial CFS, CFS and MDD than in normal controls, and significantly greater in CFS than in those with partial CFS and MDD. We found significant and positive correlations between serum IgM levels directed against nitro-BSA and symptoms of the FibroFatigue scale, i.e. aches and pain and muscular tension. There was also a strong positive correlation between serum IgM titers directed against nitro-BSA and an index of increased gut permeability ("leaky gut"), i.e. serum IgM and IgA directed against LPS of different gram-negative enterobacteria. **Discussion:** The abovementioned results indicate that both CFS and MDD are accompanied by a) an increased gut permeability which has allowed an exaggerated passage of BSA through a compromised epithelial barrier; b) increased nitrosative stress which has induced damage to BSA; and c) an IgM-mediated immune response which is directed against the nitro-BSA neoepitopes. Nitrosative stress is one of the factors underpinning the comorbidity and clinical overlap between CFS and MDD. © 2008 *Neuroendocrinology Letters*.

Jason L.A., Torres-Harding S., Maher K., Reynolds N., Brown M., Sorenson M., Donalek J., Corradi K., Fletcher M.A., Lu T.

Baseline cortisol levels Predict treatment outcomes in chronic fatigue syndrome nonpharmacologic clinical trial

2008 *Journal of Chronic Fatigue Syndrome* 14 (4); 39 – 59

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650326516&partnerID=40>

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Objective: Understanding how nonpharmacologic interventions differentially affect the subgroups of patients with chronic fatigue syndrome (CFS) might provide insights into the pathophysiology of this illness. In this exploratory study, baseline measures of normal versus abnormal cortisol were compared on a variety of immune markers and other self-report measures. Normal versus abnormal cortisol ratings were used as predictors in a nurse-delivered nonpharmacologic intervention. **Methods:** Participants diagnosed with CFS were assigned to 6-month nonpharmacologic interventions. Individuals were classified as having abnormal or normal cortisol levels on the basis of scores over the five testing times. Cortisol levels were considered abnormal if they continued to rise, were flat, or were at abnormally low over time. **Results:** Across interventions, those with abnormal cortisol at the baseline appeared not to improve over time, whereas those with normal baseline cortisol evidenced improvements on a number of immunologic and self-report measures. **Conclusion:** It appears that, in subgroups of individuals with CFS, baseline cortisol markers are associated with outcome trajectories

for nonpharmacologic treatment trials. The implications of these findings are discussed. © 2008 by Informa Healthcare USA, Inc.

Hokama Y., Empey-Campora C., Hara C., Higa N., Siu N., Lau R., Kuribayashi T., Yabusaki K.
Acute phase phospholipids related to the cardiolipin of mitochondria in the sera of patients with chronic fatigue syndrome (CFS), chronic ciguatera fish poisoning (CCFP), and other diseases attributed to chemicals, gulf war, and marine toxins

2008 Journal of Clinical Laboratory Analysis 22 (2); 99 – 105

<http://www.scopus.com/inward/record.url?eid=2-s2.0-42149179439&partnerID=40>

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This study examined 328 CFS sera in a study with 17 CCFP, 8 Gulf War Veterans (GWV), 24 Prostate Cancer (PC), and 52 normal sera in the modified Membrane Immunobead Assay (MIA) procedure for CTX. Three hundred and twenty-eight CFS patients' sera were examined by the modified MIA with purified MAb-CTX and 91.2% gave a titre $\geq 1:40$. 76% of the 17 CCFP sera samples and 100% of the 8 GWV sera samples also had a titre $\geq 1:40$. 92.3% of 52 normal sera showed titres of 1:20 or less, while 4 gave titres of $\geq 1:40$. In addition, 41 sera were examined for Anti-Cardiolipin (aCL) by a commercial ELISA procedure with 87.8% demonstrating IgM, IgM+IgA, or IgM + IgG aCL antibodies. These results showed mostly the IgM aCL antibody alone in the sera samples. In addition, 41 serum samples were examined for aCL, with 37 showing positive for aCL, representing 90.2% positive for the three disease categories examined: CFS, CCFP and GWV. Examination for antiMitochondrial-M2 autoantibody (aM-M2) in 28 patients (CFS (18), CCFP (5), and GWV (5)) was negative for aM-M2. Inhibition analysis with antigens, CTX, CFS "Acute Phase Lipids", commercial Cardiolipin (CL) and 1,2-Dipalmitoyl-sn-Glycero-3-[Phospho-L-Serine] (PS) and antibodies, MAb-CTX and aCL from patients' serum show that the phospholipids in CL and CTX are antigenically indistinguishable with antibodies MAb-CTX and CFS-aCL. Preliminary chemical analyses have shown the lipids to be phospholipids associated with CL of the mitochondria. We designate this "Acute Phase Lipid" comparable to "Acute Phase Proteins" (C-reactive protein (CRP) and Serum Amyloid A (SAA)) in inflammatory conditions. © 2008 Wiley-Liss, Inc.

Dietert R.R., Dietert J.M.

Possible role for early-life immune insult including developmental immunotoxicity in chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME)

2008 Toxicology 247 (1); 61 - 72

<http://www.scopus.com/inward/record.url?eid=2-s2.0-41449104483&partnerID=40>

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Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) in some countries, is a debilitating disease with a constellation of multi-system dysfunctions primarily involving the neurological, endocrine and immune systems. While substantial information is available concerning the complex dysfunction-associated symptoms of CFS, environmental origins of the disease have yet to be determined. Part of the dilemma in identifying the cause(s) has been the focus on biomarkers (hormones, neurotransmitters, cytokines, infectious agents) that are contemporary with later-life CFS episodes. Yet, recent investigations on the origins of environmental diseases of the neurological, endocrine, reproductive, respiratory and immune systems suggest that early life toxicologic and other insults are pivotal in producing later-life onset of symptoms. As with autism and childhood asthma, CFS can also occur in children where the causes are certainly early-life events. Immune dysfunction is recognized as part of the CFS phenotype but has received comparatively less attention than aberrant neurological or endocrine function. However, recent research results suggest that early life immune

insults (ELII) including developmental immunotoxicity (DIT), which is induced by xenobiotics, may offer an important clue to the origin(s) of CFS. The developing immune system is a sensitive and novel target for environmental insult (xenobiotic, infectious agents, stress) with major ramifications for postnatal health risks. Additionally, many prenatal and early postnatal neurological lesions associated with postnatal neurobehavioral diseases are now recognized as linked to prenatal immune insult and inflammatory dysregulation. This review considers the potential role of ELII including DIT as an early-life component of later-life CFS. © 2008 Elsevier Ireland Ltd. All rights reserved.

Bassi N., Amital D., Amital H., Doria A., Shoenfeld Y.
Chronic fatigue syndrome: Characteristics and possible causes for its pathogenesis

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-41149130206&partnerID=40>

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Chronic fatigue syndrome is a heterogeneous disorder with unknown pathogenesis and etiology, characterized by disabling fatigue, difficulty in concentration and memory, and concomitant skeletal and muscular pain. Several mechanisms have been suggested to play a role in CFS, such as excessive oxidative stress following exertion, immune imbalance characterized by decreased natural killer cell and macrophage activity, immunoglobulin G subclass deficiencies (IgG1, IgG3) and decreased serum concentrations of complement component. Autoantibodies were also suggested as a possible factor in the pathogenesis of CFS. Recent studies indicate that anti-serotonin, anti-microtubule-associated protein 2 and anti-muscarinic cholinergic receptor 1 may play a role in the pathogenesis of CFS. It has been demonstrated that impairment in vasoactive neuropeptide metabolism may explain the symptoms of CFS.

Aspler A.L., Bolshin C., Vernon S.D., Broderick G.
Evidence of inflammatory immune signaling in chronic fatigue syndrome: A pilot study of gene expression in peripheral blood

2008 Behavioral and Brain Functions 4

<http://www.scopus.com/inward/record.url?eid=2-s2.0-54349114732&partnerID=40>

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Background: Genomic profiling of peripheral blood reveals altered immunity in chronic fatigue syndrome (CFS) however interpretation remains challenging without immune demographic context. The object of this work is to identify modulation of specific immune functional components and restructuring of co-expression networks characteristic of CFS using the quantitative genomics of peripheral blood. Methods: Gene sets were constructed a priori for CD4+ T cells, CD8+ T cells, CD19+ B cells, CD14+ monocytes and CD16+ neutrophils from published data. A group of 111 women were classified using empiric case definition (U.S. Centers for Disease Control and Prevention) and unsupervised latent cluster analysis (LCA). Microarray profiles of peripheral blood were analyzed for expression of leukocyte-specific gene sets and characteristic changes in co-expression identified from topological evaluation of linear correlation networks. Results: Median expression for a set of 6 genes preferentially up-regulated in CD19+ B cells was significantly lower in CFS ($p = 0.01$) due mainly to PTPRK and TSPAN3 expression. Although no other gene set was differentially expressed at $p < 0.05$, patterns of co-expression in each group differed markedly. Significant co-expression of CD14+ monocyte with CD16+ neutrophil ($p = 0.01$) and CD19+ B cell sets ($p = 0.00$) characterized CFS and fatigue phenotype groups. Also in CFS was a significant negative correlation between CD8+ and both CD19+ up-regulated ($p = 0.02$) and NK gene sets ($p = 0.08$). These patterns were absent in controls.

Conclusion: Dissection of blood microarray profiles points to B cell dysfunction with coordinated immune activation supporting persistent inflammation and antibody-mediated NK cell modulation of T cell activity. This has clinical implications as the CD19+ genes identified could provide robust and biologically meaningful basis for the early detection and unambiguous phenotyping of CFS. © 2008 Aspler et al; licensee BioMed Central Ltd.

Seishima M., Mizutani Y., Shibuya Y., Arakawa C.

Chronic fatigue syndrome after human parvovirus B19 infection without persistent viremia

2008 *Dermatology* 216 (4); 341 - 346

<http://www.scopus.com/inward/record.url?eid=2-s2.0-43049146216&partnerID=40>

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Background: It is unclear how often chronic fatigue syndrome (CFS) appears after human parvovirus B19 (B19) infection and whether prolonged B19 viremia or some other factors cause CFS. Objectives: To determine how often CFS appears after B19 infection and whether prolonged B19 DNA presence, antibody production and persistently reduced complement levels occur in CFS patients after B19 infection. Methods: Clinical findings were examined in 210 patients after B19 infection, and CH50, C3 and C4 levels were determined. B19 DNA and antibodies to B19 were also tested in 38 patients' sera including 3 with CFS. Results: Serum B19 DNA disappeared after 4-5 months in all 18 patients tested. There are no differences in B19 DNA-positive period between patients with and without persistent symptoms. IgM antibody titers to B19 became reduced after 2 months in all 38 patients. Complement levels persistently decreased in a greater proportion of patients with persistent symptoms. Conclusions: The present study suggests that we should consider the possibility of CFS after B19 infection and that CFS may be derived from several aspects other than prolonged B19 DNA presence in sera. Copyright © 2008 S. Karger AG.

Schur E.A., Noonan C., Buchwald D.S.

Prospective study of body mass index, weight change, and fatigue in acute infectious mononucleosis

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-39749198373&partnerID=40>

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Objective: To examine the influence of body mass index (BMI) and weight change on fatigue severity and failure to recover in individuals with acute infectious mononucleosis. Methods: We prospectively studied 148 individuals presenting with a positive monospot test. We obtained measured weights and vitality subscale scores from the Short Form-36 Health Survey (SF-36) at the index visit and at 6 months. Results: The mean age of the participants was 21 years and 24% were overweight or obese. During acute illness, overweight and obese participants had an adjusted odds ratio for low vitality scores of 2.9 (confidence interval 1.2-7.1) compared to normal weight subjects. Neither index BMI nor 6-month weight gain was significantly associated with prolonged fatigue or failure to recover. Conclusion: Overweight and obese patients with acute infectious mononucleosis are more likely to experience severe fatigue. In contrast, neither baseline weight nor weight gain appear to impede recovery. Copyright © by The Haworth Press, Inc. All rights reserved.

Nicolson G.L., Nicolson N.L., Haier J.

Chronic fatigue syndrome patients subsequently diagnosed with Lyme disease *Borrelia burgdorferi*: Evidence for Mycoplasma species coinfections

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650339823&partnerID=40>

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Objective: We examined the blood of 48 North American chronic fatigue syndrome (CFS) patients subsequently diagnosed with Lyme disease (*Borrelia burgdorferi* infection) and compared these with 50 North American CFS patients without evidence of *Borrelia burgdorferi* infections for presence of Mycoplasma species coinfections using forensic polymerase chain reaction. **Results:** We found that 68.75% of CFS/Lyme patients show evidence of Mycoplasma coinfections (odds ratio [OR] = 41.8; confidence limits [CL] = 11.3-155; and p .001) compared with controls, whereas 50% of CFS patients without a diagnosis of Lyme disease show Mycoplasma coinfections (OR = 19.0; CL = 5.3-69; and p .001) compared with controls. Because CFS patients without a diagnosis of Lyme disease have a high prevalence of one of four Mycoplasma species and a majority show evidence of multiple infections, we examined CFS/Lyme patients' blood for various Mycoplasma species. We found that CFS patients with Lyme disease mostly had single species Mycoplasma infections (OR = 31.7; CL = 8.6-116; and p .001) with a preponderance of Mycoplasma fermentans infections (50% of patients; OR = 59.0; CL = 7.6-460; and p .001), whereas the most commonly found Mycoplasma species in CFS patients without Lyme disease was Mycoplasma pneumoniae (34% of patients; OR = 14.94; CL = 3.3-69; and p .001). **Conclusions:** The results indicate that a subset of CFS patients show evidence of infection with *Borrelia burgdorferi*, and a large fraction of these patients were also infected with Mycoplasma fermentans and to a lesser degree with other Mycoplasma species. © 2008 by Informa Healthcare USA, Inc.

Maes M., Leunis J.-C.

Normalization of leaky gut in chronic fatigue syndrome (CFS) is accompanied by a clinical improvement: Effects of age, duration of illness and the translocation of LPS from gram-negative bacteria

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Background: There is now evidence that an increased translocation of LPS from gram negative bacteria with subsequent gut-derived inflammation, i.e. induction of systemic inflammation and oxidative & nitrosative stress (IO&NS), is a new pathway in chronic fatigue syndrome (CFS). **Methods:** The present study examines the serum concentrations of IgA and IgM to LPS of gram-negative enterobacteria, i.e. *Hafnia Alvei*; *Pseudomonas Aeruginosa*, *Morganella Morganii*, *Pseudomonas Putida*, *Citrobacter Koseri*, and *Klebsiella Pneumoniae* in CFS patients both before and after intake of natural anti-inflammatory and anti-oxidative substances (NAIOSs), such as glutamine, N-acetyl cysteine and zinc, in conjunction with a leaky gut diet during 10-14 months. We measured the above immune variables as well as the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale in 41 patients with CFS before and 10-14 months after intake of NAIOSs. **Results:** Subchronic intake of those NAIOSs significantly attenuates the initially increased IgA and IgM responses to LPS of gram negative bacteria. Up to 24 patients showed a significant clinical improvement or remission 10-14 months after intake of NAIOSs. A good clinical response is significantly predicted by attenuated IgA and IgM responses to LPS, the younger age of the patients, and a shorter duration of illness (< 5 years). **Discussion:** The results show that normalization of the IgA and IgM responses to translocated LPS may predict clinical outcome in CFS. The results support the view that a weakened tight junction barrier with subsequent gut-derived inflammation is a novel pathway in CFS and that it is a new target for drug development

in CFS. Meanwhile, CFS patients with leaky gut can be treated with specific NAIOSs and a leaky gut diet. © 2008 Neuroendocrinology Letters.

Kerr J.R., Matthey D.L.

Preexisting psychological stress predicts acute and chronic fatigue and arthritis following symptomatic parvovirus b19 infection

2008 Clinical Infectious Diseases 46 (9)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-42549134141&partnerID=40>

Department of Cellular and Molecular Medicine, St. George's University of London, London; Sir Joseph Hotung Centre for Musculoskeletal Disorders, St. George's University of London, London; Staffordshire Rheumatology Centre, University Hospital of North Staffordshire, Stoke on Trent, United Kingdom; St George's University of London, Cranmer Terrace, London SW17 0RE, United Kingdom

Background. Psychological stress is thought to be an important factor in the pathogenesis of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Therefore, we sought to examine this relationship in the context of parvovirus B19 infection. **Methods.** Thirty-nine patients with laboratory-documented acute parvovirus B19 infection were asked to complete questionnaires on negative life events, perceived stress, and negative affect relevant to the time of onset of parvovirus infection and during the preceding 12 months. These scores were combined into an overall stress index, which was then examined for associations with particular parvovirus-associated symptoms at acute infection and during the ensuing 1-3 years. Additional characteristics monitored included presence of parvovirus antibodies and nucleic acid, cortisol level, dehydroepiandrosterone level, autoantibodies, levels of a range of serum cytokines, and human leukocyte antigen class I and II alleles. **Results.** Stress index was significantly associated with development of fatigue during the acute phase of parvovirus B19 infection and also with chronic fatigue and arthritis occurring 1-3 years following acute parvovirus B19 infection. Logistic regression that included all clinical variables indicated that a high stress index at the time of onset of infection was the primary predictor of CFS/ME 1-3 years following acute parvovirus B19 infection (odds ratio, 25.7; 95% confidence interval, 1.7-121.9; P<.005). **Conclusions.** We report a highly significant association between psychological stress and development of acute and chronic fatigue and arthritis several years following laboratory-documented acute parvovirus B19 infection. © 2008 by the Infectious Diseases Society of America. All rights reserved.

Grinde B.

Is chronic fatigue syndrome caused by a rare brain infection of a common, normally benign virus?

2008 Medical Hypotheses 71 (2); 270 – 274

<http://www.scopus.com/inward/record.url?eid=2-s2.0-45849132029&partnerID=40>

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Chronic fatigue syndrome (CFS) is a disabling disease of unknown aetiology. A variety of factors have been suggested as possible causes. Although the symptoms and clinical findings are heterogeneous, the syndrome is sufficiently distinct, at least in relation to the more obvious cases, that a common explanation seems likely. In this paper, it is proposed that the disease is caused by a ubiquitous, but normally benign virus, e.g., one of the circoviruses. Circoviruses are chronically present in a majority of people, but are rarely tested for diagnostically. Normally these viruses do not penetrate the blood-brain barrier, but exceptions have been reported, and related viruses cause disease in the central nervous system of animals. The flu-like illness that often precedes the onset of CFS may either suppress immune function, causing an increased viremia, and/or lower the blood-brain barrier. In both cases the result may be that a virus already present in the blood enters the brain. It is well known that zoonotic viruses typically are more malignant than viruses with a long history of host-virus evolution. Similarly, a virus reaching an unfamiliar organ may cause particular problems. © 2008 Elsevier Ltd. All rights reserved.

Faulkner S., Smith A.

A longitudinal study of the relationship between psychological distress and recurrence of upper respiratory tract infections in chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-39649111560&partnerID=40>

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Objectives. Previous research has found that chronic fatigue syndrome (CFS) patients report increased susceptibility to upper respiratory tract illnesses (URTIs) when compared with healthy volunteers. This study aimed to replicate and extend this research by investigating the role of psychological distress (stress and negative mood) in the recurrence of URTIs in CFS patients as well as its role in the recurrence of CFS symptoms. **Design.** A 15-week diary study. **Methods.** Measures of psychological stress, negative mood, recurrence of URTIs and symptoms were recorded each week for a 15-week period. CFS patients (N = 21), who had been assessed and diagnosed according to the Oxford criteria, were recruited from the Cardiff Chronic Fatigue Clinic and compared with a matched group of healthy controls (N = 18). Frequency of occurrence of infectious illness and the relationship between psychological stress/negative mood and occurrence of illness were assessed. **Results.** CFS patients reported more URTIs than the controls. Stress scores (and negative mood) were significantly higher in the week prior to the occurrence of URTIs than in weeks when no subsequent illness occurred. High levels of psychological stress also preceded the severity of reported symptoms of fatigue in the CFS group. **Conclusions.** CFS patients reported more frequent URTIs than healthy controls and these recurrences were preceded by high levels of psychological stress. High levels of stress were also associated with greater subsequent fatigue. Possible explanations of these results are discussed. © 2008 The British Psychological Society.

Chia J.K.S., Chia A.Y.

Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach

2008 Journal of Clinical Pathology 61 (1); 43 – 48

<http://www.scopus.com/inward/record.url?eid=2-s2.0-38449085803&partnerID=40>

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Background and Aims: The aetiology for chronic fatigue syndrome (CFS) remains elusive although enteroviruses have been implicated as one of the causes by a number of studies. Since most CFS patients have persistent or intermittent gastrointestinal (GI) symptoms, the presence of viral capsid protein 1 (VP1), enterovirus (EV) RNA and culturable virus in the stomach biopsy specimens of patients with CFS was evaluated. **Methods:** 165 consecutive patients with CFS underwent upper GI endoscopies and antrum biopsies. Immunoperoxidase staining was performed using EV-specific monoclonal antibody (mAb) or a control mAb specific for cytomegalovirus (CMV). RT-PCR ELISA was performed on RNA extracted from paraffin sections or samples preserved in RNA later. Biopsies from normal stomach and other gastric diseases served as controls. 75 samples were cultured for EV. **Results:** 135/165 (82%) biopsies stained positive for VP1 within parietal cells, whereas 7/34 (20%) of the controls stained positive ($p < 0.001$). CMV mAb failed to stain any of the biopsy specimens. Biopsies taken from six patients at the onset of the CFS/abdominal symptoms, and 2-8 years later showed positive staining in the paired specimens. EV RNA was detected in 9/24 (37%) paraffin-embedded biopsy samples; 1/21 controls had detectable EV RNA ($p < 0.01$); 1/3 patients had detectable EV RNA from two samples taken 4 years apart; 5 patient samples showed transient growth of non-cytopathic enteroviruses. **Conclusion:** Enterovirus VP1, RNA and non-cytopathic viruses were detected in the stomach biopsy specimens of CFS patients with chronic abdominal complaints. A significant subset of CFS patients may have a chronic, disseminated, non-cytolytic form of enteroviral infection, which could be diagnosed by stomach biopsy.

Beqaj S.H., Lerner A.M., Fitzgerald J.T.

Immunoassay with cytomegalovirus early antigens from gene products p52 and CM2 (UL44 and UL57) detects active infection in patients with chronic fatigue syndrome

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Pathgroup Labs., Nashville, TN, United States; Departments of Medicine, William Beaumont Hospital, Wayne State University School of Medicine, Royal Oak, MI, United States; Department of Medical Education, University of Michigan School of Medicine, Ann Arbor, MI, United States; 32804 Pierce St, Beverly Hills, MI 48025, United States

Aims: To investigate whether the use of recombinant early antigens for detection of antibodies to human cytomegalovirus (HCMV) gene products CM 2 (UL44, UL57) and p52 (UL44) is specific in the diagnosis and differentiation of active HCMV infection in a subset of patients with chronic fatigue syndrome (CFS), a diagnosis which is often missed by the current ELISA assay that uses crude viral lysate antigen. **Methods:** At a single clinic from 1999 to 2001, a total of 4774 serological tests were performed in 1135 patients with patients using two immunoassays, Copalis and ELISA. The Copalis immunoassay utilised HCMV early gene products of UL44 and UL57 recombinant antigens for detection of HCMV IgM antibody, and viral capsid antigen for detection of HCMV IgG antibody. The ELISA immunoassay utilised viral crude lysate as antigen for detection of both HCMV IgG and IgM. **Results:** 517 patients (45.6%) were positive for HCMV IgG by both assays. Of these, 12 (2.2%) were positive for HCMV(V) IgM serum antibody by HCMV ELISA assay, and 61 (11.8%) were positive for IgM HCMV serum antibody by Copalis assay. The Copalis assay that uses HCMV early recombinant gene products CM2 (UL44, UL57) and p52 (UL44) in comparison with ELISA was 98% specific. **Conclusions:** Immunoassays that use early antigen recombinant HCMV CM2 and p52 are five times more sensitive than HCMV ELISA assay using viral lysate, and are specific in the detection and differentiation of active HCMV infection in a subset of patients with CFS.

Maes M., Mihaylova I., Leunis J.-C. Increased serum IgA and IgM against LPS of enterobacteria in chronic fatigue syndrome (CFS): Indication for the involvement of gram-negative enterobacteria in the etiology of CFS and for the presence of an increased gut-intestinal permeability 2007 *Journal of Affective Disorders* 99 01-Mar 237 240 <http://www.scopus.com/inward/record.url?eid=2-s2.0-33847238471&partnerID=40> MCare4U Outpatient Clinics, Belgium; Department of Psychiatry, Vanderbilt University Nashville, TN, United States; Laboratory Ategis, Waver, Belgium There is now evidence that chronic fatigue syndrome (CFS) is accompanied by immune disorders and by increased oxidative stress. The present study has been designed in order to examine the serum concentrations of IgA and IgM to LPS of gram-negative enterobacteria, i.e. *Hafnia alvei*; *Pseudomonas aeruginosa*, *Morganella morganii*, *Proteus mirabilis*, *Pseudomonas putida*, *Citrobacter koseri*, and *Klebsiella pneumoniae* in CFS patients, patients with partial CFS and normal controls. We found that the prevalences and median values for serum IgA against the LPS of enterobacteria are significantly greater in patients with CFS than in normal volunteers and patients with partial CFS. Serum IgA levels were significantly correlated to the severity of illness, as measured by the FibroFatigue scale and to symptoms, such as irritable bowel, muscular tension, fatigue, concentration difficulties, and failing memory. The results show that enterobacteria are involved in the etiology of CFS and that an increased gut-intestinal permeability has caused an immune response to the LPS of gram-negative enterobacteria. It is suggested that all patients with CFS should be checked by means of the IgA panel used in the present study and accordingly should be treated for increased gut permeability. © 2006 Elsevier B.V. All rights reserved.

Maes M., Coucke F., Leunis J.-C.

Normalization of the increased translocation of endotoxin from gram negative enterobacteria (leaky gut) is accompanied by a remission of chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-37849019360&partnerID=40>

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There is now evidence that chronic fatigue syndrome (CFS) is accompanied by an increased translocation of endotoxins from gram-negative enterobacteria through the gut wall, as demonstrated by increased prevalences and median values for serum IgM and IgA against the endotoxins of gram-negative enterobacteria. This condition can also be described as increased gut permeability or leaky gut and indicates intestinal mucosal dysfunction (IMD). Here we report a case of a 13 year old girl with CFS who showed very high values for serum IgM against the LPS of some enterobacteria and signs of oxidative and nitrosative stress, activation of the inflammatory response system, and IgG3 subclass deficiency. Upon treatment with specific antioxidants and a "leaky gut diet", which both aim to treat increased gut permeability, and immunoglobins intravenously, the increased translocation of the LPS of gram negative enterobacteria normalized and this normalization was accompanied by a complete remission of the CFS symptoms. © 2007 Neuroendocrinology Letters.

Lerner A.M., Beqaj S.H., Deeter R.G., Fitzgerald J.T.

Valacyclovir treatment in Epstein-Barr virus subset chronic fatigue syndrome: Thirty-six months follow-up

2007 In Vivo 21 (5); 707 - 714

<http://www.scopus.com/inward/record.url?eid=2-s2.0-35649008849&partnerID=40>

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Background: We hypothesized that subset classification of Epstein-Barr virus (EBV) in chronic fatigue syndrome (CFS) is required. At first, a blinded-random placebo-controlled trial of valacyclovir in EBV CFS subset was performed (Group 1), and this EBV subset was followed for thirty-six months (Group 2). Patients were given valacyclovir at 14.3 mg/ kg every 6 hours. The validated Energy Index (EI) point score assessing physical functional capacity, Holter monitor, multigated (radionuclide) MUGA rest/stress ventriculographic examination, EBV serum IgM viral capsid antibodies (VCA), and EBV early antigen diffuse (EA) were followed. After six-months, Group 1 CFS patients receiving valacyclovir experienced an increased mean least square EI point score + 1.12 units (122 kcal/day), while the placebo cohort increased + 0.42 EI units (65 kcal/day). EI point scores at Group 2 increased progressively. Sinus tachycardias decreased and abnormal cardiac wall motion improved. Serum antibody titers to EBV VCA IgM decreased. Patients resumed normal activities.

Ledina D., Bradaric N., Milas I., Ivic I., Brncic N., Kuzmicic N.

Chronic fatigue syndrome after Q fever

2007 Medical Science Monitor 13 (7)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34447122551&partnerID=40>

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Background: Q fever is a common and acute but rare chronic zoonosis caused by *Coxiella burnetii*. Its acute form manifests as atypical pneumonia, flu-like syndrome, or hepatitis. Some authors observed symptoms of chronic fatigue in a small number of patients after the acute phase of Q fever; in many cases serological assay confirmed the activity of *Coxiella burnetii* infection. The effect of antibiotic therapy on post-Q-fever fatigue syndrome has not been studied in south-east Europe thus far. Case Reports: Three patients are presented with post-Q-fever fatigue syndrome. All fulfilled the CDC criteria for chronic fatigue syndrome. IgA antibodies to phase I of the growth cycle of *Coxiella burnetii* were positive in two patients and negative in one. Two patients were treated with doxycycline for two weeks in the acute phase of illness and one with a combination of erythromycin and gentamycin. After 4-12 months they developed post-Q-fever fatigue syndrome and were treated with intracellular active antibiotics (fluoroquinolones and tetracycline) for 3-12 months. Efficacy of the treatment was observed in two patients, but in one patient the results were not encouraging. Conclusions: These results suggest the possibility of the involvement of *Coxiella burnetii* infection in the evolution of chronic fatigue syndrome. This is the first report on post-Q-fever fatigue syndrome in Mediterranean countries. Evidence of IgA antibodies to phase I of the growth cycle of *Coxiella burnetii* is not a prerequisite for establishing a diagnosis of CFS. The recommendation of antibiotic treatment in post-Q-fever fatigue syndrome requires further investigation. © Med Sci Monit, 2007.

Appel S., Chapman J., Shoenfeld Y.

Infection and vaccination in chronic fatigue syndrome: Myth or reality?

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847343458&partnerID=40>

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Chronic fatigue syndrome (CFS) is characterized by severe disabling fatigue lasting for more than 6 months associated with physical and mental disturbances such as headache, arthralgia, myalgia, memory impairment, sore throat and tender lymph nodes. The exact pathogenesis is still unknown. Several models were proposed to explain its etiology including chronic infection, endocrine dysfunction, autonomic imbalance, depression, decreased immunity states and an aberrant reaction to infection. No convincing evidence was found to support any of the suggested pathogenic mechanisms. The current concept is that CFS pathogenesis is a multi factorial condition in which an infective agent cause an aberrant immune response characterized by a shift to Th-2 dominant response. When the response fails to be switched-off, a chronic immune activation occurs and clinically expressed as the symptomatology of CFS. Vaccinations are used in order to stimulate the immune system to induce a persistent immunity against the favorable antigens. Several syndromes that contain chronic fatigue as one of their symptoms, such as "Gulf war syndrome" and macrophagic myofasciitis were related to vaccinations. Can vaccinations induce the aberrant immune response of CFS? Little is known about this issue. There are some reports on CFS occurring after vaccination, but few prospective and retrospective studies failed to find such an association. A working group of the Canadian Laboratory Center for Disease Control (LCDC) that was founded in order to examine the suspected association between CFS and vaccinations concluded that there is no evidence that relates CFS to vaccination. Further studies are requested to examine this issue since it is very conceivable that if infection can lead to CFS, vaccination may also lead to it in the same immune-mediated pathogenesis.

ter Wolbeek M., van Doornen L.J.P., Kavelaars A., van de Putte E.M., Schedlowski M., Heijnen C.J.
Longitudinal analysis of pro- and anti-inflammatory cytokine production in severely fatigued adolescents

2007 Brain, Behavior, and Immunity 21 (8); 1063 – 1074

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34748826761&partnerID=40>

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In the adolescent population, fatigue is associated with somatic complaints, unrefreshing sleep, cognitive disturbances and symptoms of depression and anxiety. This pattern of symptoms resembles the one described in chronic fatigue syndrome (CFS). Since immunological alterations have been reported in CFS patients, we wondered whether also severely fatigued girls from a healthy population would show comparable alterations in psychological and immunological parameters. We tested this hypothesis in a longitudinal design, allowing a reliable assessment of the participants' characteristic immune status. Groups of severely fatigued (N = 67) and non-fatigued (N = 61) participants were selected. Severely fatigued girls reported more depressive symptoms, anxiety, reduced sleep quality, and somatic and CFS-related symptoms than non-fatigued participants across three measurements during one year (T1: spring, T2: autumn, T3: spring). In contrast, no group differences in mitogen-induced cytokine production or T-cell proliferation in vitro or in leukocyte subset counts were observed. Although absolute cytokine production and cell counts were affected by seasonal variation, the within-subject values, relatively to the rest of the participants, were fairly stable. Data from a small group of CFS patients (N = 11) showed similarities in self-reported complaints between CFS patients and fatigued participants. Interestingly, CFS patients showed a distinct immune profile when compared to the severely fatigued or non-fatigued participants, i.e. increased levels of anti-inflammatory cytokines (IL-10, decreased IFN- γ /IL-10 ratio) and reduced levels of pro-inflammatory cytokines (IL-6, TNF- α) over all three time points analyzed. These results show that, although overlap in symptomatology between the general population and patients with CFS was observed, only CFS patients show a skewing of the cytokine balance towards an anti-inflammatory profile. © 2007 Elsevier Inc. All rights reserved.

Richards R.S., Wang L., Jelinek H.

Erythrocyte Oxidative Damage in Chronic Fatigue Syndrome

2007 Archives of Medical Research 38 (1); 94 – 98

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33845424640&partnerID=40>

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Background: It has been hypothesized that a link exists between erythrocyte metabolism (particularly redox metabolism) and erythrocyte shape and that both are related to erythrocyte deformability. The aim of this research is to confirm the results of earlier studies and to investigate a correlation between erythrocyte morphology and erythrocyte oxidative damage in chronic fatigue syndrome (CFS). Methods: Reduced glutathione (GSH), malondialdehyde (MDA), methemoglobin (metHb) and 2,3-diphosphoglyceric acid (2,3-DPG) were measured in 31 patients suffering from CFS and 41 healthy control subjects. Scanning electron microscopic studies of the erythrocytes from both groups were also carried out. Results: There was evidence of oxidative damage in CFS with statistically significant increases in 2,3-DPG (p <0.05), metHb (p <0.005) and MDA (p <0.01). The CFS patients in this study also had significantly more stomatocytes in their blood than the normal subjects (p <0.005). Conclusions: There is a strong likelihood that the increase in erythrocyte antioxidant activity is associated with the presence of stomatocytes. The results of this study provide further evidence for

the role of free radicals in the pathogenesis of CFS and a link between erythrocyte metabolism and erythrocyte shape. © 2007 IMSS.

Pall M.L.

Nitric oxide synthase partial uncoupling as a key switching mechanism for the NO/ONOO- cycle

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Short-term stressors, capable of increasing nitric oxide levels, act to initiate cases of illnesses including chronic fatigue syndrome, multiple chemical sensitivity, fibromyalgia and posttraumatic stress disorder. These stressors, acting primarily through the nitric oxide product, peroxynitrite, are thought to initiate a complex vicious cycle mechanism, known as the NO/ONOO- cycle that is responsible for chronic illness. The complexity of the NO/ONOO- cycle raises the question as to whether the mechanism that switches on this cycle is this complex cycle itself or whether a simpler mechanism is the primary switch. It is proposed here that the switch involves a combination of two variable switches, the increase of nitric oxide synthase (NOS) activity and the partial uncoupling of the NOS activity, with uncoupling caused by a tetrahydrobiopterin (BH4) deficiency. NOS uncoupling causes the NOS enzymes to produce superoxide, the other precursor of peroxynitrite, in place of nitric oxide. Thus partial uncoupling will cause NOS proteins to act like peroxynitrite synthases, leading, in turn to increased NF- κ B activity. Peroxynitrite is known to oxidize BH4, and consequently partial uncoupling may initiate a vicious cycle, propagating the partial uncoupling over time. The combination of high NOS activity and BH4 depletion will lead to a potential vicious cycle that may be expected to switch on the larger NO/ONOO- cycle, thus producing the symptoms and signs of chronic illness. The role of peroxynitrite in the NO/ONOO- cycle also implies that such uncoupling is part of the chronic phase cycle mechanism such that agents that lower uncoupling will be useful in treatment. © 2007 Elsevier Ltd. All rights reserved.

Mihaylova I., DeRuyter M., Rummens J.-L., Bosmans E., Maes M.

Decreased expression of CD69 in chronic fatigue syndrome in relation to inflammatory markers: Evidence for a severe disorder in the early activation of T lymphocytes and natural killer cells

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There is some evidence that patients with chronic fatigue syndrome (CFS) suffer from immune abnormalities, such as immune activation and decreased immune cell responsivity upon polyclonal stimuli. This study was designed to evaluate lymphocyte activation in CFS by using a CD69 expression assay. CD69 acts as a costimulatory molecule for T- and natural killer (NK) cell activation. We collected whole blood from CFS patients, who met CDC criteria, and healthy volunteers. The blood samples were stimulated with mitogens during 18 h and the levels of activated T and NK cells expressing CD69 were measured on a Coulter Epics flow cytometer using a three color immunofluorescence staining protocol. The expression of the CD69 activation marker on T cells (CD3+, CD3+CD4+, and CD3+CD8+) and on NK cells (CD45+CD56+) was significantly lower in CFS patients than in healthy subjects. These differences were significant to the extent that a significant diagnostic performance was obtained, i.e. the area under the ROC curve was around 89%. No differences either in the number of leukocytes or in the number or percentage of lymphocytes, i.e. CD3, CD4, CD8 and CD19, could be found between CFS patients and the controls. Patients with CFS

show defects in T- and NK cell activation. Since induction of CD69 surface expression is dependent on the activation of the protein kinase C (PKC) activation pathway, it is suggested that in CFS there is a disorder in the early activation of the immune system involving PKC. © 2007 Neuroendocrinology Letters.

Maes M., Mihaylova I., Leunis J.-C.

Increased serum IgM antibodies directed against phosphatidyl inositol (Pi) in chronic fatigue syndrome (CFS) and major depression: Evidence that an IgM-mediated immune response against Pi is one factor underpinning the comorbidity between both CFS and depression

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Major depression and chronic fatigue syndrome (CFS) are accompanied by signs of oxidative and nitrosative stress (O&NS) and an inflammatory response. Phosphatidyl inositol (Pi) is thought to play a role in depression. The aim of the present study is to examine whether depression and CFS are characterized by an IgM-mediated immune response directed against Pi. Toward this end, this study examines the serum IgM antibodies directed against Pi in 14 patients with major depression, 14 patients with CFS, 14 subjects with partial CFS, and in 11 normal controls. We found that the prevalence and mean value for the serum IgM levels directed against Pi were significantly greater in patients with major depression and CFS than in normal controls and patients with partial CFS. There were significant and positive correlations between serum IgM levels directed against Pi and two symptoms of the FibroFatigue Scale, i.e. fatigue and depression. The results show that an IgM-related immune response directed against Pi may occur in both depression and CFS and may play a role in the pathophysiology of the key symptom of CFS and major depression. It is suggested that the above disorders in Pi result from increased O&NS in both depression and CFS. Autoanti-Pi antibodies may have biological effects, for example, by changing inositol 1,4,5-triphosphate (IP3), phosphatidylinositol-4,5-bisphosphate (PIP2), diacylglycerol and phosphatidylinositol-3,4,5-triphosphate (PIP3) production, thus interfering with intracellular signalling processes. Future research in major depression and CFS should focus on the functional consequences of the immune responses directed against Pi. © 2007 Neuroendocrinology Letters.

Maes M., Mihaylova I., Kubera M., Bosmans E.

Not in the mind but in the cell: Increased production of cyclo-oxygenase-2 and inducible NO synthase in chronic fatigue syndrome

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Chronic fatigue syndrome (CFS) is a medically unexplained disorder, characterized by profound fatigue, infectious, rheumatological and neuropsychiatric symptoms. There is, however, some evidence that CFS is accompanied by signs of increased oxidative stress and inflammation in the peripheral blood. This paper examines the role of the inducible enzymes cyclo-oxygenase (COX-2) and inducible NO synthase (iNOS) in the pathophysiology of CFS. Toward this end we examined the production of COX-2 and iNOS by peripheral blood lymphocytes (PBMC) in 18 CFS patients and 18 normal volunteers and examined the relationships between those inflammatory markers and the severity of illness as measured by means of the FibroFatigue scale and the production of the transcription factor nuclear factor kappa beta (NF- κ B). We found that the production of COX-2 and iNOS was significantly higher in CFS patients than in normal controls. There were significant and positive intercorrelations between COX-2, iNOS and NF- κ B and between COX-2 and iNOS, on the one hand, and the severity of illness, on the other. The production of COX-2 and iNOS by PBMCs was

significantly related to aches and pain, muscular tension, fatigue, concentration difficulties, failing memory, sadness and a subjective experience of infection. The results suggest that a) an intracellular inflammatory response in the white blood cells plays an important role in the pathophysiology of CFS; b) the inflammatory response in CFS is driven by the transcription factor NF κ B; c) symptoms, such as fatigue, pain, cognitive defects and the subjective feeling of infection, indicates the presence of a genuine inflammatory response in CFS patients; and d) CFS patients may be treated with substances that inhibit the production of COX-2 and iNOS. © 2007 Neuroendocrinology Letters.

Maes M., Mihaylova I., Bosmans E.

Not in the mind of neurasthenic lazybones but in the cell nucleus: Patients with chronic fatigue syndrome have increased production of nuclear factor kappa beta

2007 Neuroendocrinology Letters 28 (4); 456 – 462

<http://www.scopus.com/inward/record.url?eid=2-s2.0-35348845895&partnerID=40>

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There is now some evidence that chronic fatigue syndrome is accompanied by an activation of the inflammatory response system and by increased oxidative and nitrosative stress. Nuclear factor kappa beta (NF κ B) is the major upstream, intracellular mechanism which regulates inflammatory and oxidative stress mediators. In order to examine the role of NF κ B in the pathophysiology of CFS, this study examines the production of NF κ B p50 in unstimulated, 10 ng/mL TNF- α (tumor necrosis factor alpha) and 50 ng/mL PMA (phorbolmyristate acetate) stimulated peripheral blood lymphocytes of 18 unmedicated patients with CFS and 18 age-sex matched controls. The unstimulated (F= 19.4, df=1/34, p=0.0002), TNF- α (F=14.0, df=1/34, p=0.0009) and PMA (F=7.9, df=1/34, p=0.008) stimulated production of NF κ B were significantly higher in CFS patients than in controls. There were significant and positive correlations between the production of NF κ B and the severity of illness as measured with the FibroFatigue scale and with symptoms, such as aches and pain, muscular tension, fatigue, irritability, sadness, and the subjective feeling of infection. The results show that an intracellular inflammatory response in the white blood cells plays an important role in the pathophysiology of CFS and that previous findings on increased oxidative stress and inflammation in CFS may be attributed to an increased production of NF κ B. The results suggest that the symptoms of CFS, such as fatigue, muscular tension, depressive symptoms and the feeling of infection reflect a genuine inflammatory response in those patients. It is suggested that CFS patients should be treated with antioxidants, which inhibit the production of NF κ B, such as curcumin, N-Acetyl-Cysteine, quercetin, silimarin, lipoic acid and omega-3 fatty acids. © 2007 Neuroendocrinology Letters.

Takahashi T., Yu F., Zhu S.-J., Moriya J., Sumino H., Morimoto S., Yamaguchi N., Kanda T.

Beneficial effect of Brewers' yeast extract on daily activity in a murine model of chronic fatigue syndrome

2006 Evidence-based Complementary and Alternative Medicine 3 (1); 109 – 115

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The aim of this study was to assess the effect of Brewers' yeast extract (BYE) on daily activity in a mouse model of chronic fatigue syndrome (CFS). CFS was induced by repeated injection of Brucella abortus (BA) antigen every 2 weeks. BYE was orally administered to mice in a dose of 2 g per kg per day for 2 weeks before injecting BA and for 4 weeks thereafter. We evaluated daily running activity in

mice receiving BYE as compared with that in untreated mice. Weekly variation of body weight (BW) and survival in both groups was monitored during the observation period. Spleen weight (SW), SW/BW ratio, percent splenic follicular area and expression levels of interferon- γ (IFN- γ) and interleukin-10 (IL-10) mRNA in spleen were determined in both groups at the time of sacrifice. The daily activity during 2 weeks after the second BA injection was significantly higher in the treated group than in the control. There was no difference in BW between both groups through the experimental course. Two mice in the control died 2 and 7 days after the second injection, whereas no mice in the treated group died. Significantly decreased SW and SW/BW ratio were observed in the treated mice together with elevation of splenic follicular area. There were suppressed IFN- γ and IL-10 mRNA levels in spleens from the treated mice. Our results suggest that BYE might have a protective effect on the marked reduction in activity following repeated BA injection via normalization of host immune responses. © The Author (2006). Published by Oxford University Press. All rights reserved.

Siegel S.D., Antoni M.H., Fletcher M.A., Maher K., Segota M.C., Klimas N.
Impaired natural immunity, cognitive dysfunction, and physical symptoms in patients with chronic fatigue syndrome: preliminary evidence for a subgroup?

2006 Journal of Psychosomatic Research 60 (6); 559 – 566

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646774706&partnerID=40>

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Objective: The diagnostic criteria of chronic fatigue syndrome (CFS) define a heterogeneous population composed of several subgroups. Past efforts to identify subgroup markers have met with mixed success. This study was designed to examine natural killer cell activity (NKCA) as a potential subgroup marker by comparing the clinical presentations of CFS patients with and without clinically reduced NKCA. Methods: Forty-one female CFS patients were classified into having either low or normal NKCA levels. These subgroups were then compared on objective measures of cognitive functioning and subjective assessments of fatigue, vigor, cognitive impairment, and daytime dysfunction. Results: Relative to CFS patients in the normal-NKCA subgroup, low-NKCA patients reported less vigor, more daytime dysfunction, and more cognitive impairment. In addition, low-NKCA patients performed less on objective measures of cognitive functioning relative to normal-NKCA patients. Conclusions: The results are offered as preliminary evidence in support of using NKCA as an immunological subgroup marker in CFS. Findings are also discussed in terms of known associations between dysregulated immune functions, somatic symptoms, and psychological stress. © 2006 Elsevier Inc. All rights reserved.

McDermott C., Richards S.C.M., Thomas P.W., Montgomery J., Lewith G.

A placebo-controlled, double-blind, randomized controlled trial of a natural killer cell stimulant (BioBran MGN-3) in chronic fatigue syndrome

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Background: Previous research has suggested that natural killer (NK) cell activity may be reduced in patients with chronic fatigue syndrome (CFS). Aim: To evaluate the effectiveness of a putative NK cell stimulant, BioBran MGN-3, in reducing fatigue in CFS patients. Design: Randomized, double-blind,

placebo-controlled trial. Methods: We recruited 71 patients with CFS (according to the Centers for Disease Control 1994 criteria) attending an out-patient specialist CFS service. Participants were given oral BioBran MGN-3 for 8 weeks (2 g three times per day) or placebo equivalent. The primary outcome measure was the Chalder physical fatigue score. Self-reported fatigue measures, self-assessment of improvement, change in key symptoms, quality of life, anxiety and depression measures were also included. Results: Data were complete in 64/71 patients. Both groups showed marked improvement over the study duration, but without significant differences. Mean improvement in the Chalder fatigue score (physical scale) was 0.3 (95%CI -2.6 to 3.2) lower in the BioBran group. Discussion: The findings do not support a specific therapeutic effect for BioBran in CFS. The improvement showed by both groups over time highlights the importance of placebo controls when evaluating interventions in CFS. © 2006 Oxford University Press.

Maes M., Mihaylova I., Leunis J.-C.

Chronic fatigue syndrome is accompanied by an IgM-related immune response directed against neopeptides formed by oxidative or nitrosative damage to lipids and proteins

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33845967496&partnerID=40>

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There is now some evidence that chronic fatigue syndrome (CFS) is accompanied by signs of oxidative stress and by a decreased antioxidant status. The aim of the present study was to examine whether CFS is accompanied by an immune response to neopeptides of a variety of modified lipids and proteins indicating damage caused by oxidative and nitrosative stress. Toward this end we examined serum antibodies to fatty acids (oleic, palmitic and myristic acid), by-products of lipid peroxidation, i.e. azelaic acid and malondialdehyde (MDA), acetylcholine, S-farnesyl-L-cysteine, and N-oxide modified amino-acids in 14 patients with CFS, 14 subjects with partial CFS and 11 normal controls. We found that the prevalences and mean values for the serum IgM levels directed against oleic, palmitic and myristic acid, MDA, azelaic acid, S-farnesyl-L-cysteine, and the N-oxide derivatives, nitro-tyrosine, nitro-phenylalanine, nitro-arginine, nitro-tryptophan, and nitro-cysteine were significantly greater in CFS patients than in normal controls, whereas patients with partial CFS took up an intermediate position. There were significant and positive correlations between the serum IgM levels directed against fatty acids, MDA and azelaic acid and the above N-oxide-derivates and the severity of illness (as measured by the FibroFatigue scale) and symptoms, such as aches and pain, muscular tension and fatigue. The results show that CFS is characterized by an IgM-related immune response directed against disrupted lipid membrane components, by-products of lipid peroxidation, S-farnesyl-L-cysteine, and NO-modified amino-acids, which are normally not detected by the immune system but due to oxidative and nitrosative damage have become immunogenic. © Neuroendocrinology Letters.

Maes M., Mihaylova I., De Ruyter M.

Lower serum zinc in Chronic Fatigue Syndrome (CFS): Relationships to immune dysfunctions and relevance for the oxidative stress status in CFS

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-31844436261&partnerID=40>

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The present study examines serum zinc concentrations in patients with chronic fatigue syndrome (CFS) versus normal volunteers. Serum zinc levels were determined by means of an atomic absorption method. We found that serum zinc was significantly lower in the CFS patients than in the normal

controls. There was a trend toward a significant negative correlation between serum zinc and the severity of CFS and there was a significant and negative correlation between serum zinc and the subjective experience of infection. We found that serum zinc was significantly and negatively correlated to the increase in the alpha2 protein fraction and positively correlated to decreases in the expression of mitogen-induced CD69+ (a T cell activation marker) on CD3+ as well as CD3+CD8+ T cells. These results show that CFS is accompanied by a low serum zinc status and that the latter is related to signs of inflammation and defects in early T cell activation pathways. Since zinc is a strong anti-oxidant, the present results further support the findings that CFS is accompanied by increased oxidative stress. The results of these reports suggest that some patients with CFS should be treated with specific antioxidants, including zinc supplements. © 2005 Elsevier B.V. All rights reserved.

Kodama M., Kodama T.

Four problems with the clinical control of interstitial pneumonia, or chronic fatigue syndrome, using the megadose vitamin C infusion system with dehydroepiandrosterone-cortisol annex

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Since 1996 in our clinic, the regular practice of megadose vitamin C infusion with dehydroepiandrosterone-cortisol annex and the continuous intake of erythromycin and chloramphenicol have been found useful for the clinical control of the autoimmune disease interstitial pneumonia, also known as chronic fatigue syndrome. The long-term use of these two systems for the treatment of the autoimmune disease has led to the emergence of four problems of theoretical or practical importance, as described below: i) Should maintenance of the above core treatments be continued for prophylactic purposes in the absence of acute signs of pneumonia? Evidence indicated that their use was essential to arrest the dynamic activity of an intrapulmonary bacterial colony in the immunodeficient host, and that the 5-year survival rate of interstitial pneumonia patients would have been worse without the prophylactic practice of the 2 treatments. ii) Evidence was presented to suggest that the activity of the intrapulmonary bacterial colony was becoming less responsive because of the emergence of a drug-resistant mutant bacterium. The introduction of new antibiotics (kanamycin) was found to improve the acute signs of pneumonia. iii) The bone marrow function of one male patient with interstitial pneumonia was found to decline during the observation period of 9 years. It was speculated that his bone marrow, like his lungs, was in the course of fibrosis. iv) One female patient was diagnosed with breast cancer in the course of interstitial pneumonia treatment - an example indicating that the persistence of an autoimmune disease in an elderly subject might be associated with the emergence of malignancy. Dehydroepiandrosterone was shown to promote the recovery of hepatic function in the course of cancer chemotherapy with cyclophosphamide. The beneficial effect of the adrenal androgen was dose-dependent. The significance of this finding is discussed in the light of the steroid carcinogenesis concept. The reasoning behind the view that interstitial pneumonia and chronic fatigue syndrome are one disease is also discussed.

Katafuchi T.

Possible involvement of brain cytokines and 5-HT system in chronic fatigue syndrome

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We have recently developed an animal model for fatigue induced by intraperitoneal (i.p.) injection of synthetic double-stranded RNAs, polyriboinosinic:polyribocytidylic acid (poly I:C) in rats. This animal model shows a decrease in daily amounts of spontaneous running wheel activity to about 60% of the

preinjection level, and increase in interferon- γ (IFN- γ) mRNA in rat hypothalamic nuclei and cortex for more than a week. In addition, serotonin transporter (5-HTT), which is induced by IFN- γ , also increased in the same regions. In vivo brain microdialysis demonstrated a decrease in 5-HT levels in the prefrontal cortex after poly I:C, which was blocked by a selective 5-HT reuptake inhibitor, fluoxetine. Furthermore, the poly I:C-induced suppression of the running wheel activity was attenuated by a 5-HT_{1A} receptor agonist, but not by 5-HT₂ and 5-HT₃ receptor agonists. Possible involvement of IFN- γ and 5-HT system in the mechanisms of the poly I:C-induced fatigue as well as CFS was discussed. © 2005 Elsevier B.V. All rights reserved.

Fremont M., Vaeyens F., Herst C.V., De Meirleir K., Englebienne P.
Antiviral pathway deregulation of chronic fatigue syndrome induces nitric oxide production in immune cells that precludes a resolution of the inflammatory response

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Chronic fatigue syndrome (CFS) is a poorly defined medical condition diagnosed by exclusion, which, besides severe chronic fatigue as the hallmark symptom, involves inflammatory and immune activation stigma. Although viral infections are not systematically found in CFS patients, the type I interferon antiviral pathway has been repeatedly shown to be activated in peripheral blood mononuclear cells (PBMC) of the most afflicted patients. An abnormal truncated form of ribonuclease L (37-kDa RNase L) is also found in the PBMC of CFS patients and this protein has been proposed as a biological marker for CFS. Recently, the levels of this abnormal protein have been significantly correlated to the extent of inflammatory symptoms displayed by CFS patients. We report here that active double-stranded RNA-dependent kinase (PKR) is expressed and activated in parallel to the presence of the 37-kDa RNase L and to an increase in nitric oxide production by immune cells. However, PKR upregulation results also in a significant increase followed by a decrease in caspase 3 activity for the samples containing the highest levels of 37-kDa RNase L. This caspase 3 downregulation does not result from increased expression of the anti-apoptotic proteins Bcl-2 and Bcl-XL. These results therefore suggest that chronic inflammation due to excess nitric oxide production plays a role in CFS and that the normal resolution of the inflammatory process by NF- κ B activation and apoptotic induction is impaired. These observations draw new directions for the therapeutic approach of CFS. © Copyright by The Haworth Press, Inc. All rights reserved.

Broderick G., Craddock R.C., Whistler T., Taylor R., Klimas N., Unger E.R.
Identifying illness parameters in fatiguing syndromes using classical projection methods

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Objectives: To examine the potential of multivariate projection methods in identifying common patterns of change in clinical and gene expression data that capture the illness state of subjects with unexplained fatigue and nonfatigued control participants. Methods: Data for 111 female subjects was

examined. A total of 59 indicators, including multidimensional fatigue inventory (MFI), medical outcome Short Form 36 (SF-36), Centers for Disease Control and Prevention (CDC) symptom inventory and cognitive response described illness. Partial least squares (PLS) was used to construct two feature spaces: one describing the symptom space from gene expression in peripheral blood mononuclear cells (PBMC) and one based on 117 clinical variables. Multiplicative scatter correction followed by quantile normalization was applied for trend removal and range adjustment of microarray data. Microarray quality was assessed using mean Pearson correlation between samples. Benjamini-Hochberg multiple testing criteria served to identify significantly expressed probes. Results: A single common trend in 59 symptom constructs isolates of nonfatigued subjects from the overall group. This segregation is supported by two co-regulation patterns representing 10% of the overall microarray variation. Of the 39 principal contributors, the 17 probes annotated related to basic cellular processes involved in cell signaling, ion transport and immune system function. The single most influential gene was sestrin 1 (SESN1), supporting recent evidence of oxidative stress involvement in chronic fatigue syndrome (CFS). Dominant variables in the clinical feature space described heart rate variability (HRV) during sleep. Potassium and free thyroxine (T4) also figure prominently. Conclusion: Combining multiple symptom, gene or clinical variables into composite features provides better discrimination of the illness state than even the most influential variable used alone. Although the exact mechanism is unclear, results suggest a common link between oxidative stress, immune system dysfunction and potassium imbalance in CFS patients leading to impaired sympatho-vagal balance strongly reflected in abnormal HRV. © 2006 Future Medicine Ltd.

Yaqob A., Danersund A., Stejskal V.D.M., Lindvall A., Hudecek R., Lindh U.
Metal-specific lymphocyte reactivity is down-regulated after dental metal replacement
2006 Neuroendocrinology Letters 27 (01-Feb); 189 – 197
<http://www.scopus.com/inward/record.url?eid=2-s2.0-33745648728&partnerID=40>

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Objectives: This study was done to evaluate the results and clinical relevance of an optimized lymphocyte proliferation test, MELISA®, for metal-induced inflammation in patients with CFS-like symptoms. The treatment of patients consisted of the replacement of incompatible dental materials (RID) together with supportive anti-oxidant therapy. Design of the study: 513 patients were tested by MELISA® at the beginning of the study. Out of this group, 248 patients were available for follow-up MELISA® after RID. Methods: In MELISA®, lymphocytes are isolated from the blood and cultivated with different metal salts in tissue culture medium containing 10% inactivated human AB+ serum or autologous serum. After 5 days, the presence of metal-reactive lymphocytes are measured by isotope labelling of newly formed DNA in growing lymphoblasts and evaluated by calculating the Stimulation Index. Results: Nickel was the most common sensitizer, followed by inorganic mercury, thimerosal, lead, cadmium, palladium and gold. After RID treatment, a decrease of metal-specific lymphocyte responses in patients who reacted to metals at the beginning of the study could be observed. The cultivation of lymphocytes in autologous and homologous serum did not significantly affect the results. Simultaneous, the health status of patients improved as well. Conclusions: Replacement of incompatible dental materials resulted in down-regulation of metal-induced lymphocyte sensitivity in vitro, as well as in the improvement of health status of majority of patients with unspecific CFS-like symptoms. © Neuroendocrinology Letters.

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Azithromycin in Chronic Fatigue Syndrome (CFS), an analysis of clinical data

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Background: CFS is a clinical state with defined symptoms, but undefined cause. The patients may show a chronic state of immune activation and treatment with an antibiotic in this subgroup has been suggested. Methods: In a retrospective study, the response of CFS patients to azithromycin, an antibiotic and immunomodulating drug, has been scored from the patients records and compared with clinical and laboratory data. Azithromycin was not the first choice therapy, but offered when the effect of counseling and L-carnitine was considered insufficient by the patient and the clinician. Results: Of the 99 patients investigated, 58 reported a decrease in the symptoms by the use of azithromycin. These responding patients had lower levels of plasma acetylcarnitine. Conclusion: The efficacy of azithromycin in the responsive patients could be explained by the modulating effect on a chronic primed state of the immune cells of the brain, or the activated peripheral immune system. Their lower acetylcarnitine levels may reflect a decreased antioxidant defense and/or an increased consumption of acetylcarnitine caused by oxidative stress. © 2006 Vermeulen and Scholte; licensee BioMed Central Ltd.

Moss-Morris R., Spence M.

To "lump" or to "split" the functional somatic syndromes: Can infectious and emotional risk factors differentiate between the onset of chronic fatigue syndrome and irritable bowel syndrome?

2006 Psychosomatic Medicine 68 (3); 463 - 469

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33746078524&partnerID=40>

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OBJECTIVES: Recent academic debate has centered on whether functional somatic syndromes should be defined as separate entities or as one syndrome. The aim of this study was to investigate whether there may be significant differences in the etiology or precipitating factors associated with two common functional syndromes, irritable bowel syndrome (IBS) and chronic fatigue syndrome (CFS). **METHODS:** We prospectively studied 592 patients with an acute episode of *Campylobacter* gastroenteritis and 243 with an acute episode of infectious mononucleosis who had no previous history of CFS or IBS. At the time of infection, patients completed a baseline questionnaire that measured their levels of distress using the Hospital Anxiety and Depression scale. At 3- and 6-month follow-up, they completed questionnaires to determine whether they met published diagnostic criteria for chronic fatigue (CF), CFS, and/or IBS. **RESULTS:** The odds of developing IBS were significantly greater post-*Campylobacter* than post-infectious mononucleosis at both 3- (odds ratio, 3.45 [95% confidence interval (CI), 1.75-6.67]) and 6- (2.22 [95% CI, 1.11-6.67]) month follow-up. In contrast, the odds for developing CF/CFS were significantly greater after infectious mononucleosis than after *Campylobacter* at 3 (2.77 [95% CI, 1.08-7.11]) but not 6 (1.48 [95% CI, 0.62-3.55]) months postinfection. Anxiety and depression were the strongest predictors of CF/CFS, whereas the nature of the infection was the strongest predictor of IBS. **CONCLUSIONS:** These results support the argument to distinguish between postinfectious IBS and CFS. The nature of the precipitating infection appears to be important, and premorbid levels of distress appear to be more strongly associated with CFS than IBS, particularly levels of depression. Copyright © 2006 by the American Psychosomatic Society.

Lundell K., Qazi S., Eddy L., Uckun F.M.
Clinical activity of folinic acid in patients with chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33745914957&partnerID=40>

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A high incidence of severe B-cell immunodeficiency and chronic reactivated Epstein-Barr virus (EBV) infection in patients with chronic fatigue syndrome (CFS) is reported herein. Of the 58 patients evaluated, 100% had evidence of prior EBV exposure and 72% had evidence for reactivated EBV infection. Notably, 94% of CFS patients had B-cell immunodeficiency with a marked depletion of their CD19+IgM+ mature B-lymphocyte population. A remarkable 81% of CFS patients experienced subjective improvement of their symptoms after treatment with folinic acid (CAS 58-05-9, leucovorin). The findings provide unprecedented evidence that CFS frequently is a folinic acid responsive clinical entity accompanied by B-cell immunodeficiency and inappropriate antibody responses to EBV. © ECV A. Editio Cantor Verlag, Aulendorf.

Iwakami E., Arashima Y., Kato K., Komiya T., Matsukawa Y., Ikeda T., Arakawa Y., Oshida S.
Treatment of chronic fatigue syndrome with antibiotics: Pilot study assessing the involvement of *Coxiella burnetii* infection

2006 *Internal Medicine* 44 (12); 1258 - 1263

<http://www.scopus.com/inward/record.url?eid=2-s2.0-31444442117&partnerID=40>

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Objective: To examine whether *Coxiella burnetii* (*C. burnetii*) is involved in chronic fatigue syndrome (CFS), we administered tetracycline antibiotics to subjects with CFS, and followed changes in clinical symptoms, PCR findings, and *C. burnetii* antibody titers. **Patients and methods:** The subjects were 8 patients with CFS and 213 with nonspecific complaints such as chronic fatigue and low-grade fever for several months or longer but not meeting the diagnostic criteria for CFS. All were examined for *C. burnetii* infection by nested PCR and the indirect immunofluorescence test (IF). **Results:** Four CFS patients (the CFS group) and 54 controls [the post-Q fever fatigue syndrome (QFS) group] positive for *C. burnetii* were treated mainly with minocycline or doxycycline (100 mg/day) for 3 months. After treatment, all 58 patients tested negative for *C. burnetii* infection. In the CFS group, no significant difference was noted between the mean pre- and post-treatment temperatures or headache scores. Similarly, there was no significant improvement in performance status (PS) scores. In the QFS group, however, mean temperatures and headache scores were significantly decreased after treatment ($p < 0.001$). PS scores were also improved. **Conclusion:** These results suggest the possibility of direct involvement of *C. burnetii* in the pathological state of CFS to be low, despite the *C. burnetii* infection rate being high in CFS patients. This is a pilot study and further larger investigations are necessary to confirm our preliminary results.

Hickie I., Davenport T., Wakefield D., Vollmer-Conna U., Cameron B., Vernon S.D., Reeves W.C., Lloyd A.

Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: Prospective cohort study

2006 British Medical Journal 333 (7568); 575 – 578

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33748925038&partnerID=40>

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Objective: To delineate the risk factors, symptom patterns, and longitudinal course of prolonged illnesses after a variety of acute infections. **Design:** Prospective cohort study following patients from the time of acute infection with Epstein-Barr virus (glandular fever), *Coxiella burnetii* (Q fever), or Ross River virus (epidemic polyarthritis). **Setting:** The region surrounding the township of Dubbo in rural Australia, encompassing a 200 km geographical radius and 104 400 residents. **Participants:** 253 patients enrolled and followed at regular intervals over 12 months by self report, structured interview, and clinical assessment. **Outcome measures:** Detailed medical, psychiatric, and laboratory evaluations at six months to apply diagnostic criteria for chronic fatigue syndrome. Premorbid and intercurrent illness characteristics recorded to define risk factors for chronic fatigue syndrome. Self reported illness phenotypes compared between infective groups. **Results:** Prolonged illness characterised by disabling fatigue, musculoskeletal pain, neurocognitive difficulties, and mood disturbance was evident in 29 (12%) of 253 participants at six months, of whom 28 (11%) met the diagnostic criteria for chronic fatigue syndrome. This post-infective fatigue syndrome phenotype was stereotyped and occurred at a similar incidence after each infection. The syndrome was predicted largely by the severity of the acute illness rather than by demographic, psychological, or microbiological factors. **Conclusions:** A relatively uniform post-infective fatigue syndrome persists in a significant minority of patients for six months or more after clinical infection with several different viral and non-viral micro-organisms. Post-infective fatigue syndrome is a valid illness model for investigating one pathophysiological pathway to chronic fatigue syndrome.

Chapenko S., Krumina A., Kozireva S., Nora Z., Sultanova A., Viksna L., Murovska M.
Activation of human herpesviruses 6 and 7 in patients with chronic fatigue syndrome.

2006 Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology 37 (Suppl 1)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34548020257&partnerID=40>

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BACKGROUND: Human herpesvirus 6 (HHV-6) and 7 (HHV-7) have been suggested as possible triggering agents for chronic fatigue syndrome (CFS). **OBJECTIVES:** To determine the possible association of HHV-6 and HHV-7 infections with CFS. **STUDY DESIGN:** The prevalence of latent/persistent and active viral infections by nPCR, characteristic of HHV-6 variants using restriction endonuclease analysis and changes of lymphocyte subsets in peripheral blood by laser flow-cytometry in 17 CFS patients was examined. In addition, 12 patients with unexplained chronic fatigue and 20 blood donors (BD) were studied. **RESULTS:** No difference in prevalence of latent/persistent single viral infections between the patients and BD was found but dual infection rate was significantly higher in CFS patients. Active HHV-6 and dual (HHV-6 + HHV-7) infections were detected in CFS patients only and frequency of HHV-7 reactivation was also significantly higher in these patients. HHV-6 variant B was predominant in CFS patients (12/13). The changes of immunological parameters in CFS patients with active dual infection were characterized by significant decrease of CD3+ and CD4+ T cells, significant increase of CD95+ cells and decrease of CD4+/CD8+ ratio. **CONCLUSIONS:** HHV-6 and

HHV-7 may be involved in the pathogenesis of CFS and reactivation of both viruses may provoke changes in the phenotype of circulating lymphocytes.

Bond P.A., Dinan T.G.

Antibodies to Herpes simplex types 1 and 2 in chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33748550668&partnerID=40>

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Background: It has been suggested that Herpes simplex virus (HSV) could play a role in the aetiology of chronic fatigue syndrome (CFS). An immune system that has been compromised, could account for HSV reactivating or infecting for the first time, and also being insufficiently under control in the body. Another consequence of inadequate control could be that several strains of HSV could simultaneously infect the body. Objectives: To look for the presence of antibodies to HSV-1 and HSV-2 in patients with CSF and in controls. The presence of antibodies to both types of HSV could reflect infection by multiple strains of HSV. Methods: Antibodies to HSV-1 and HSV-2 were measured in sera from 27 CSF patients and 26 age- and sex-matched controls. CFS was diagnosed using the CDC criteria. Results: More CFS patients had antibodies to HSV-1, HSV-2 and both types simultaneously, than did the controls (all $p < .019$). Conclusions: More CFS patients have antibodies to both HSV-1 and HSV-2 than do controls. The possibility that multiple strains could recombine to form more virulent strains or ones able to cause different forms of illness is discussed. © 2006 by The Haworth Press, Inc. All rights reserved.

Tomoda A., Joudoi T., Rabab E.-M., Matsumoto T., Park T.H., Miike T.

Cytokine production and modulation: Comparison of patients with chronic fatigue syndrome and normal controls

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-16244380191&partnerID=40>

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We studied cytokine production in 15 patients with chronic fatigue syndrome (CFS) and 23 controls. CFS patients' peripheral blood mononuclear cells were cultured with lipopolysaccharide or phytohemagglutinin. Enzymatic immunoassay indicated cytokine concentration in culture supernatants. CFS patients showed significantly lower mRNA levels and transforming growth factor-beta1 (TGF- β 1) production. Cytokine dysregulation affects CFS pathogenesis. TGF- β 1 may aid treatment because it affects CFS inflammatory characteristics. © 2005 Elsevier Ireland Ltd. All rights reserved.

Staines D.R.

Therapeutic and preventive interventions for postulated vasoactive neuropeptide autoimmune fatigue-related disorders

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-22544457914&partnerID=40>

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Major advances have been made in understanding the relatively novel group of vasoactive (vasodilatory) neuropeptides (VNs) in humans. VNs comprise a novel but expanding group of

substances having immunoregulation, inflammation modulation, neurotransmitter, neurotrophic, hormonal and metabolic functions. These substances may control gene expression for mRNA for themselves and their receptors. They have complex relationships with gaseous and other neurotransmitters and xenobiotic substances. Theoretical arguments have implicated these substances in autoimmune phenomena resulting in fatigue-related conditions such as chronic fatigue syndrome (CFS), sudden infant death syndrome (SIDS), fibromyalgia (FM) and Gulf War syndrome (GWS) but remain unproven. As well as possibly spontaneous onset, the precipitating causes of VN autoimmune dysfunction are likely to be a combination of genetic predisposition, infection and xenobiotic substances. Therapeutic and preventive possibilities for postulated VN autoimmune conditions will be influenced by the complex pathophysiology underpinning them. Some speculative possibilities are VN substitution/replacement, preservation of biological effect, epigenetic DNA modifications, plasma exchange, anti-cholinesterases, e.g., pyridostigmine, corticosteroids and other drug treatments, thymectomy, intravenous immunoglobulin and anti-idiotypic antibodies, and CpG/DNA vaccines. Prevention and treatment of possible VN autoimmune fatigue-related disorders may prove to be important areas for future research and development.

Staines D.R.

Do vasoactive neuropeptides and heat shock proteins mediate fatigue-related autoimmune disorders?

2005 Medical Hypotheses 64 (3); 539 - 542

<http://www.scopus.com/inward/record.url?eid=2-s2.0-11144317886&partnerID=40>

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Autoimmune dysfunction of certain vasoactive neuropeptides may be implicated in a range of disorders associated with fatigue like states (chronic fatigue syndrome, Gulf War syndrome) and even sudden infant death syndrome. These substances have neurotrophic, neuroregulatory, and neurotransmission functions, as well as that of immune modulators and hormones. They exert significant control over carbohydrate and lipid metabolism. The hypothesis is that because these substances have vital and indispensable roles in cellular processes, loss or compromise of these roles would lead to predictable and severe cellular and systemic effects. The important roles of certain VNs make them a vulnerable target for autoimmune dysfunction. They are known to be associated with heat shock proteins for intracellular functioning with which they may form immunostimulating complexes. While peptide-HSP complexes are a relatively new area for research, this paper asserts that attention could be focused on these substances and complexes in an effort to elucidate a number of perplexing fatigue-associated disorders. © 2004 Elsevier Ltd. All rights reserved.

Snell C.R., Vanness J.M., Strayer D.R., Stevens S.R.

Exercise capacity and immune function in male and female patients with chronic fatigue syndrome

2005 In Vivo 19 (2); 387 - 390

<http://www.scopus.com/inward/record.url?eid=2-s2.0-16344380759&partnerID=40>

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Hyperactivation of an unwanted cellular cascade by the immune-related protein RNase L has been linked to reduced exercise capacity in persons with chronic fatigue syndrome (CFS). This investigation compares exercise capacities of CFS patients with deregulation of the RNase L pathway and CFS patients with normal regulation, while controlling for potentially confounding gender effects. Thirty-five male and seventy-one female CFS patients performed graded exercise tests to voluntary exhaustion. Measures of peak VO₂, peak heart rate, body mass index, perceived exertion, and respiratory quotient were entered into a two-way factorial analysis with gender and immune status as independent variables. A significant multivariate main effect was found for immune status ($p < 0.01$), with no gender effect or interaction. Follow-up analyses identified VO₂peak as contributing most to the

difference. These results implicate abnormal immune activity in the pathology of exercise intolerance in CFS and are consistent with a channelopathy involving oxidative stress and nitric oxide-related toxicity.

Singal A., Kaur S., Tirkey N., Chopra K.

Green tea extract and catechin ameliorate chronic fatigue-induced oxidative stress in mice

2005 Journal of Medicinal Food 8 (1); 47 - 52

<http://www.scopus.com/inward/record.url?eid=2-s2.0-18144386888&partnerID=40>

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Chronic fatigue syndrome (CFS) is an illness characterized by persistent and relapsing fatigue, often accompanied by numerous symptoms involving various body systems. The etiology of CFS remains unclear, but a number of studies have shown that oxidative stress may be involved in its pathogenesis. The present study was designed to investigate the protective effect of green tea extract (GTE) and catechin in the mouse model of CFS. Animals were subjected to a forced swimming test session of 6 minutes every day for 7 days: a significant increase in immobility time on successive days represented the CFS in mice. Biochemical analysis revealed that the chronic swim test significantly increased lipid peroxidation levels and decreased glutathione levels in mouse whole-brain homogenate. Treatment with GTE (25 or 50 mg/kg, i.p.) and catechin (50 or 100 mg/kg, i.p.) for 7 days reversed the increase in immobility time. Protection was correlated with the lowered levels of lipid peroxidation and restoration of reduced glutathione levels in the brains of fatigued mice. These findings strongly suggest the pivotal role of oxidative stress in the pathophysiology of CFS and that GTE and catechin could be used as potential agents in the management of CFS and warrant the inclusion of GTE and catechin in the treatment regimen of CFS patients.

Robertson M.J., Schacterle R.S., Mackin G.A., Wilson S.N., Bloomingdale K.L., Ritz J., Komaroff A.L.
Lymphocyte subset differences in patients with chronic fatigue syndrome, multiple sclerosis and major depression

2005 Clinical and Experimental Immunology 141 (2); 326 – 332

<http://www.scopus.com/inward/record.url?eid=2-s2.0-22344443910&partnerID=40>

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Chronic fatigue syndrome (CFS) is a heterogeneous disorder of unknown aetiology characterized by debilitating fatigue, along with other symptoms, for at least 6 months. Many studies demonstrate probable involvement of the central and autonomic nervous system, as well as a state of generalized immune activation and selective immune dysfunction in patients with CFS. The aim of this study was to compare the lymphocyte subsets of patients with chronic fatigue syndrome to those of patients with major depression and multiple sclerosis as well as those of healthy control subjects. No differences were found in total numbers of T cells, B cells or natural killer (NK) cells. However, differences were found in T, B and NK cell subsets. Patients with major depression had significantly fewer resting T (CD3+/CD25-) cells than the other groups. Patients with major depression also had significantly more CD20+/CD5+ B cells, a subset associated with the production of autoantibodies. Compared to patients with multiple sclerosis, patients with CFS had greater numbers of CD16+/CD3 - NK cells. Further study will be required to determine whether these alterations in lymphocyte subsets are directly

involved in the pathophysiology of these disorders, or are secondary effects of the causal agent(s).
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Nijs J., Meeus M., McGregor N.R., Meeusen R., De Schutter G., Van Hoof E., De Meirleir K.
Chronic fatigue syndrome: Exercise performance related to immune dysfunction

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-27644570648&partnerID=40>

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Purpose: To date, the exact cause of abnormal exercise response in chronic fatigue syndrome (CFS) remains to be revealed, but evidence addressing intracellular immune deregulation in CFS is growing. Therefore, the aim of this cross-sectional study was to examine the interactions between several intracellular immune variables and exercise performance in CFS patients. Methods: After venous blood sampling, subjects (16 CFS patients) performed a maximal exercise stress test on a bicycle ergometer with continuous monitoring of cardiorespiratory variables. The following immune variables were assessed: the ratio of 37 kDa Ribonuclease (RNase) L to the 83 kDa native RNase L (using a radiolabeled ligand/receptor assay), RNase L enzymatic activity (enzymatic assay), protein kinase R activity assay (comparison Western blot), elastase activity (enzymatic-colorimetric assay), the percent of monocytes, and nitric oxide determination (for monocytes and lymphocytes; flow cytometry, live cell assay). Results: Forward stepwise multiple regression analysis revealed 1) that elastase activity was the only factor related to the reduction in oxygen uptake at a respiratory exchange ratio (RER) of 1.0 (regression model: $R^2 = 0.53$, $F(1,14) = 15.5$, $P < 0.002$; elastase activity $P < 0.002$); 2) that the protein kinase R activity was the principle factor related to the reduction in workload at RER = 1.0; and 3) that elastase activity was the principle factor related to the reduction in percent of target heart rate achieved. Conclusion: These data provide evidence for an association between intracellular immune deregulation and exercise performance in patients with CFS. To establish a causal relationship, further study of these interactions using a prospective longitudinal design is required. Copyright © 2005 by the American College of Sports Medicine.

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Spinal fluid abnormalities in patients with chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-12544253722&partnerID=40>

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Arguments exist as to the cause of chronic fatigue syndrome (CFS). Some think that it is an example of symptom amplification indicative of functional or psychogenic illness, while our group thinks that some CFS patients may have brain dysfunction. To further pursue our encephalopathy hypothesis, we did spinal taps on 31 women and 13 men fulfilling the 1994 case definition for CFS and on 8 women and 5 men serving as healthy controls. Our outcome measures were white blood cell count, protein concentration in spinal fluid, and cytokines detectable in spinal fluid. We found that significantly more CFS patients had elevations in either protein levels or number of cells than healthy controls (30 versus 0%), and 13 CFS patients had protein levels and cell numbers that were higher than laboratory norms; patients with abnormal fluid had a lower rate of having comorbid depression than those with normal fluid. In addition, of the 11 cytokines detectable in spinal fluid, (i) levels of granulocyte-

macrophage colony-stimulating factor were lower in patients than controls, (ii) levels of interleukin-8 (IL-8) were higher in patients with sudden, influenza-like onset than in patients with gradual onset or in controls, and (iii) IL-10 levels were higher in the patients with abnormal spinal fluids than in those with normal fluid or controls. The results support two hypotheses: that some CFS patients have a neurological abnormality that may contribute to the clinical picture of the illness and that immune dysregulation within the central nervous system may be involved in this process.

Maheer K.J., Klimas N.G., Fletcher M.A.

Chronic fatigue syndrome is associated with diminished intracellular perforin

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-28344433673&partnerID=40>

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Chronic fatigue syndrome (CFS) is an illness characterized by unexplained and prolonged fatigue that is often accompanied by abnormalities of immune, endocrine and cognitive functions. Diminished natural killer cell cytotoxicity (NKCC) is a frequently reported finding. However, the molecular basis of this defect of in vitro cytotoxicity has not been described. Perforin is a protein found within intracellular granules of NK and cytotoxic T cells and is a key factor in the lytic processes mediated by these cells. Quantitative fluorescence flow cytometry was used to measure the intracellular perforin content in CFS subjects and healthy controls. A significant reduction in the NK cell associated perforin levels in samples from CFS patients, compared to healthy controls, was observed. There was also an indication of a reduced perforin level within the cytotoxic T cells of CFS subjects, providing the first evidence, to our knowledge, to suggest a T cell associated cytotoxic deficit in CFS. Because perforin is important in immune surveillance and homeostasis of the immune system, its deficiency may prove to be an important factor in the pathogenesis of CFS and its analysis may prove useful as a biomarker in the study of CFS. © 2005 British Society for Immunology.

Maes M., Mihaylova I., Leunis J.-C.

In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation

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There is now evidence that major depression is accompanied by decreased levels of ω -3 poly-unsaturated fatty acids (PUFA), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). There is a strong comorbidity between major depression and chronic fatigue syndrome (CFS). The present study has been carried out in order to examine PUFA levels in CFS. In twenty-two CFS patients and 12 normal controls we measured serum PUFA levels using gas chromatography and mass spectrometry. We found that CFS was accompanied by increased levels of ω -6 PUFAs, i.e. linoleic acid and arachidonic acid (AA), and mono-unsaturated fatty acids (MUFAs), i.e. oleic acid. The EPA/AA and total ω -3/ ω -6 ratios were significantly lower in CFS patients than in normal controls. The ω -3/ ω -6 ratio was significantly and negatively correlated to the severity of illness and some items of the FibroFatigue scale, i.e. aches and pain, fatigue and failing memory. The severity of illness was significantly and positively correlated to linoleic and arachidonic acid, oleic acid, ω -9 fatty acids and one of the saturated fatty acids, i.e. palmitic acid. In CFS subjects, we found significant positive correlations between the ω -3/ ω -6 ratio and lowered serum zinc levels and the lowered mitogen-

stimulated CD69 expression on CD3+, CD3+CD4+, and CD3+CD8+ T cells, which indicate defects in early T cell activation. The results of this study show that a decreased availability of ω 3 PUFAs plays a role in the pathophysiology of CFS and is related to the immune pathophysiology of CFS. The results suggest that patients with CFS should respond favourably to treatment with - amongst other things - ω 3 PUFAs, such as EPA and DHA. © Neuroendocrinology Letters.

Maes M., Mihaylova I., De Ruyter M.

Decreased dehydroepiandrosterone sulfate but normal insulin-like growth factor in chronic fatigue syndrome (CFS): Relevance for the inflammatory response in CFS

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There are a few reports that chronic fatigue syndrome (CFS) may be accompanied by changes in hormones, such as dehydroepiandrosterone (DHEA) and insulin-like growth factor (IGF1). This study examines the serum concentrations of DHEA-sulfate (DHEAS), IGF1 and IGF1 binding protein-3 (IGFBP3) in 20 patients with CFS and in 12 normal controls. The IGFBP3/IGF1 ratio was computed as an index for IGF1 availability. We found significantly lower serum DHEAS concentrations in CFS, but no significant differences either in IGF1 or the IGFBP3/IGF1 ratio between CFS patients and normal controls. The decrease in serum DHEAS was highly sensitive and specific for CFS. There were significant and positive correlations between serum DHEAS and serum zinc and the mitogen-induced expression of the CD69 molecule on CD3+CD8+ T cells (an indicator of early T cell activation). There was a significant and negative correlation between serum DHEAS and the increase in the serum alpha-2 protein fraction (an inflammatory marker). Serum IGF1, but not DHEAS, was significantly and inversely correlated to age. The results show that CFS is accompanied by lowered levels of DHEAS and that the latter may play a role in the immune (defect in the early activation of T cells) and the inflammatory pathophysiology of CFS. Copyright © 2005 Neuroendocrinology Letters.

Kennedy G., Spence V.A., McLaren M., Hill A., Underwood C., Belch J.J.F.

Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms

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The aetiology of chronic fatigue syndrome (CFS) is unknown; however, recent evidence suggests excessive free radical (FR) generation may be involved. This study investigated for the first time levels of 8-iso-prostaglandin-F₂±-isoprostanes alongside other plasma markers of oxidative stress in CFS patients and control subjects. Forty-seven patients (18 males, 29 females, mean age 48 [19-63] years) who fulfilled the Centres for Disease Control classification for CFS and 34 healthy volunteers (13 males, 21 females, 46 [19-63] years) were enrolled in the study. The CFS patients were divided into two groups; one group had previously defined cardiovascular (CV) risk factors of obesity and hypertension (group 1) and the second were normotensive and nonobese (group 2). Patients had significantly increased levels of isoprostanes (group 1, P = 0.007; group 2, P = 0.03, unpaired t test compared to controls) and oxidised low-density lipoproteins (group 2, P = 0.02) indicative of a FR attack on lipids. CFS patients also had significantly lower high-density lipoproteins (group 1, P = 0.011; group 2, P = 0.005). CFS symptoms correlated with isoprostane levels, but only in group 2 low CV risk CFS patients (isoprostanes correlated with; total symptom score P = 0.005; joint pain P = 0.002; postexertional malaise P = 0.027, Pearson). This is the first time that raised levels of the gold

standard measure of in vivo oxidative stress (isoprostanes) and their association with CFS symptoms have been reported. © 2005 Elsevier Inc. All rights reserved.

Gaab J., Rohleder N., Heitz V., Engert V., Schad T., Schurmeyer T.H., Ehlert U.
Stress-induced changes in LPS-induced pro-inflammatory cytokine production in chronic fatigue syndrome

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It has been suggested that a hypofunctional hypothalamic-pituitary-adrenal (HPA) axis in chronic fatigue syndrome could result in an exaggerated release of pro-inflammatory cytokines during stress. As pro-inflammatory cytokines are involved in the induction of sickness behavior and thus constitute a potential physiological correlate of stress-induced symptom exacerbation in chronic fatigue syndrome, we set out to evaluate the LPS-induced production of pro-inflammatory cytokines during psychosocial stress in CFS and healthy controls. Twenty-one CFS patients and 20 healthy controls matched for age and gender underwent a standardized psychosocial stress test (Trier social stress test, TSST). Adrenocorticotropic hormone (ACTH), salivary cortisol and plasma cortisol levels were measured before and repeatedly following exposure to the stressor. Lipopolysaccharide-stimulated production of interleukin-6 and tumor necrosis factor-alpha were assessed at baseline as well as 10 and 60 min after the stress test. CFS patients showed an inverse stress-induced response pattern of LPS-stimulated cytokines responses in comparison to healthy controls, i.e. stimulated cytokine production decreased shortly after stress in CFS patients, while it increased in controls. Fatigue scores and basal LPS-induced cytokine levels were significantly associated for TNF- \pm in controls and for both cytokines in CFS patients. Stress-induced changes in stimulated cytokine production were not associated with general fatigue scores in the control group, whereas in the CFS group, fatigue scores were significantly correlated with integrated levels of LPS-induced cytokines. However, partial correlations revealed that these results were due to the high correlations with basal LPS-induced cytokine levels. CFS patients do not show an exaggerated secretion of LPS-induced cytokines. Although cortisol responses to stress were normal, pro-inflammatory cytokine levels in CFS patients were significantly attenuated. Possible intracellular mechanisms, such as for example an enhanced sensitivity to inhibitory effects of glucocorticoids, a diminished responsivity to catecholaminergic stimulation, and a disruption of intracellular activation are discussed. Basal levels of stimulated pro-inflammatory IL-6 levels are generally related to fatigue scores. However, in CFS patients this association is of greater magnitude and can also be observed for TNF- \pm . © 2004 Elsevier Ltd. All rights reserved.

White E., Sherlock C.

The effect of nutritional therapy for yeast infection (candidiasis) in cases of chronic fatigue syndrome

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The objective of this study was to evaluate the effectiveness of nutritional therapy for yeast infection in cases of medically-diagnosed Chronic Fatigue Syndrome/ME. Forty participants, each with medically-diagnosed CFS/ME, received individual nutritional advice for treating yeast infection (candidiasis) over the course of one year, following an anti-candida protocol which had been used successfully in nutritional practice for twelve years. Data were generated by questionnaires from which answers enabled an assessment of nutritional status to be formulated as well as allowing scores to be calculated for CFS/ME and candidiasis. Confounding variables included stress, glucose tolerance, use of steroid treatments/ HRT/ contraceptive pill and age. The drop-out rate was high with only eighteen subjects completing the year, the main reported reason being lack of motivation to adhere to the anti-

candida diet which was part of the protocol Data analysis indicated a relatively strong positive correlation between candida and CFS/ME at the start of the study. The average fall in CFS/ME symptom scores throughout the year was 30.5%, with one participant achieving a 100% reduction in symptoms. 83% of participants experienced some reduction in CFS/ME symptoms scores. Higher than average stress scores and use of steroids/HRT/contraceptive pill all negatively impacted CFS/ME scores despite following an anti-candida protocol. Subjects aged 36 or over experienced a greater degree of improvement than younger subjects, a situation which requires further investigation. The observed study findings support the premise that nutritional therapy: specifically in the form of an anti-candida protocol, can be an effective treatment for some CFS/ME sufferers.

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Persistent parvovirus-associated chronic fatigue treated with high dose intravenous immunoglobulin

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We report a 16-year-old boy with no evidence of immunodeficiency who had a 2-year history of chronic fatigue, low grade fever and slapped-cheek rash associated with chronic parvovirus B19 viremia. Prolonged intravenous immunoglobulin therapy resulted in resolution of his symptoms and viremia. Intravenous immunoglobulin may be useful in the resolution of parvovirus viremia regardless of immune status. © 2005 Lippincott Williams & Wilkins.

Kerr J.R.

Pathogenesis of parvovirus B19 infection: Host gene variability, and possible means and effects of virus persistence

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Since conducting follow-up studies of patients with acute symptomatic parvovirus B19 infection which showed that a significant proportion of patients develop prolonged arthritis and chronic fatigue syndrome (CFS), we have become interested in the mechanisms of this phenomenon. We showed that these cases have high levels of pro-inflammatory cytokines in their circulation and that this correlates with the symptoms. However, the underlying mechanisms were not apparent, and we have used various approaches to begin studying this phenomenon. DNA polymorphisms were looked for and several were shown to be more common in these subjects compared with controls; these occur within genes of both the immune response q2[human leucocyte antigen (HLA)-DRB1, HLA-B, transforming growth factor (TGF)- β 1] and those involved in several other cellular functions (predominantly the cytoskeleton and cell adhesion). Interestingly, one particular single-nucleotide polymorphism (SNP) which is associated with symptomatic B19 infection occurs in the Ku80 gene which has recently been shown to be a B19 co-receptor. B19 persistence is probably the key to this phenomenon, and some new data are presented on short regions of sequence homology (17-26 bp) between human, mouse and rat parvoviruses and their respective hosts which occur in many host genes. This homology may provide a foothold for virus persistence and may also play a role in the genesis of disease through gene disruption. Finally, we used microarrays and TaqMan real-time polymerase chain reaction in 108 normal persons to study human gene expression in persons who are B19-seropositive versus B19-

seronegative (age- and sex-matched) to examine the hypothesis that gene regulation may be altered in subjects harbouring the B19 virus DNA. Six genes were found to be differentially expressed with roles in the cytoskeleton (SKIP, MACF1, SPAG7, FLOT1), integrin signalling (FLOT1, RASSF5), HLA class III (c6orf48), and tumour suppression (RASSF5). These results have implications not only for B19 but also for other persistent viruses as well and confirmation is required. In conclusion, these disparate findings contribute to our understanding of the pathogenesis of B19 disease. We are using these studies as a starting point to study the phenomenon of chronic immune activation following B19 infection. © 2005 Blackwell Verlag.

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GBV-C - A virus without a disease: We cannot give it chronic fatigue syndrome

2005 BMC Infectious Diseases 5

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Background: Chronic fatigue syndrome (CFS) is an illness in search of an infectious etiology. GB virus-C (GBV-C) virus is a flavivirus with cell tropism and host defense induction qualities compatible with a role in producing the syndrome. The GBV-C genome is detectable in 4% of the population and 12% of the population is seropositive. The present study evaluated the association between infection with GBV and CFS. Methods: We used a commercial EIA to detect antibodies against the GBV-C E2 protein and a quantitative real-time RT-PCR assay to detect active GBV-C infection. Sera were from a case control study of CFS in Atlanta, Georgia. The Fisher's exact two-tailed test was used for statistical analysis. Results: Two of 12 CFS patients and one of 21 controls were seropositive for prior GBV-C infection and one control had viral RNA detected, indicating active infection. The results are not statistically different. Conclusions: We found no evidence that active or past infection with GBV is associated with CFS. © 2005 Jones et al., licensee BioMed Central Ltd.

Glaser R., Padgett D.A., Litsky M.L., Baiocchi R.A., Yang E.V., Chen M., Yeh P.-E., Klimas N.G., Marshall G.D., Whiteside T., Herberman R., Kiecolt-Glaser J., Williams M.V.

Stress-associated changes in the steady-state expression of latent Epstein-Barr virus: Implications for chronic fatigue syndrome and cancer

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Antibodies to several Epstein-Barr virus (EBV)-encoded enzymes are observed in patients with different EBV-associated diseases. The reason for these antibody patterns and the role these proteins

might play in the pathophysiology of disease, separate from their role in virus replication, is unknown. In this series of studies, we found that purified EBV deoxyuridine triphosphate nucleotidohydrolase (dUTPase) can inhibit the replication of human peripheral blood mononuclear cells in vitro and upregulate the production of TNF- $\hat{I}\pm$, IL-1 \hat{I}^2 , IL-6, IL-8, and IL-10. It also enhanced the ability of natural killer cells to lyse target cells. The EBV dUTPase also significantly inhibited the replication of mitogen-stimulated lymphocytes and the synthesis of IFN- \hat{I}^3 by cells isolated from lymph nodes and spleens obtained from mice inoculated with the protein. It also produced sickness behaviors known to be induced by some of the cytokines that were studied in the in vitro experiments. These symptoms include an increase in body temperature, a decrease in body mass and in physical activity. The data provide a new perspective on how an early nonstructural EBV-encoded protein can cause immune dysregulation and produce clinical symptoms observed in patients with chronic fatigue syndrome (CFS) separate from its role in virus replication and may serve as a new approach to help identify one of the etiological agents for CFS. The data also provide additional insight into the pathophysiology of EBV infection, inflammation, and cancer. © 2004 Elsevier Inc. All rights reserved.

White P.D., Nye K.E., Pinching A.J., Yap T.M., Power N., Vleck V., Bentley D.J., Thomas J.M., Buckland M., Parkin J.M.

Immunological changes after both exercise and activity in chronic fatigue syndrome: A pilot study

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Background: The chronic fatigue syndrome (CFS) is characterized by post-exertional malaise and fatigue. We designed this pilot study to explore whether the illness was associated with alterations in immunological markers following exercise. Methods: We measured immunological markers before and up to three days after either a sub-maximal or maximal bicycle exercise test. We studied nine patients with CFS and nine age- and sex-matched healthy but sedentary controls. We also studied the same patients with CFS at home after a night's sleep and then after traveling to the study center. Results: There were no significant differences in any of the cell markers after a sub-maximal exercise test compared to a maximal test. However, we found elevated concentrations of plasma transforming growth factor beta (TGF- \hat{I}^2), even before exercise, in subjects with CFS (median (IQR) of 904 (182-1072) pg/ml) versus control's (median (IQR) of 50 (45-68) pg/ml) ($P < .001$). Traveling from home to the hospital significantly elevated TGF- \hat{I}^2 concentrations from a resting median (IQR) concentration of 1161 (130-1246) pg/ml to a median (IQR) concentration of 1364 (1155-1768) pg/ml ($P < .02$). There was also a sustained increase in plasma tumor necrosis factor alpha (TNF- $\hat{I}\pm$) after exercise in CFS patients, but not in controls ($P = .004$ for the area under the curve), although traveling had no such effect. CD3, CD4 and HLA DR-expressing lymphocyte counts were lower in CFS patients, but exercise had the same effect in both groups, causing an immediate increase in circulating cell numbers that lasted less than three hours. Conclusions: These results suggest that the relationship between physical activity and both pro-inflammatory and anti-inflammatory cytokines merits further investigation in patients with CFS. The results also emphasize the importance of defining a truly resting baseline condition in such studies. © 2004 by The Haworth Press, Inc. All rights reserved.

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Clinical and biochemical characteristics differentiating chronic fatigue syndrome from major depression and healthy control populations: Relation to dysfunction in the RNase L pathway

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Patterns of immune dysfunction have emerged in chronic fatigue syndrome (CFS) that include an immune activation state (evidenced by increased activated T lymphocytes and circulating cytokines) and poor cellular function (low natural killer (NK) cell cytotoxicity and impaired T lymphocyte response to mitogens). Therefore, the aim of the current study was to examine the relationship between clinical and functional characteristics, immune abnormalities and status of the RNase L pathway in CFS compared with healthy control and depression control populations. All study participants were assessed with respect to their general health, functional status, blood count and chemistry, biochemical and immune parameters. The CFS group (N = 66) demonstrated clinical, functional and biochemical abnormalities distinct from the healthy (N = 62) and depression (N = 51) control groups. The CFS group showed marked functional impairment compared with both control groups (P < .001) as measured by the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (P < .001). The CFS group also showed decreased cognitive performance on a computerized test battery compared to healthy (P < .001) and depression controls (P < .009) and significantly higher 37/80 kDa RNase L ratio (P < .001) compared with both control groups. The odds ratios of a 37/80 kDa RNase L ratio > 2 compared with the CFS patients were 3.9 for the healthy controls (95% confidence limit (CL) 1.0-15.2, P < .05) and 65.8 for the depression controls (95% CL 10.7-406.6, P < .001). The CFS group demonstrated low NK cell cytotoxicity compared to healthy controls (P = .045). The correlation between abnormalities in the RNase L pathway and impaired NK cell function (r = .21, P < .006) suggests that both may be part of the same underlying disease mechanism, at least in this homogeneous population of very disabled CFS patients. Healthy contact-control subjects who had exposure to CFS patients showed a number of characteristics similar to the CFS patients, including an increased mean 37/80 kDa RNase L ratio (P < .04) and prevalence of the 37/80 kDa RNase L ratio > 2 (P < .03). In these contact-control subjects, the 37/80 kDa RNase L ratio was correlated with the interferon- γ levels (r = .58, P < .02), suggestive of activation of the interferon pathway. The results of the present study support the cytokine/ immune activation model in this well-characterized CFS patient group. © 2004 by The Haworth Press, Inc. All rights reserved.

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High levels of type 2 cytokine-producing cells in chronic fatigue syndrome

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The aetiology of chronic fatigue syndrome (CFS) is not known. However, it has been suggested that CFS may be associated with underlying immune activation resulting in a Th2-type response. We measured intracellular production of interferon (IFN)- γ and interleukin (IL)-2; type 1 cytokines), IL-4

(type 2) and IL-10 (regulatory) by both polyclonally stimulated and non-stimulated CD4 and CD8 lymphocytes from patients with CFS and control subjects by flow cytometry. After polyclonal activation we found evidence of a significant bias towards Th2- and Tc2-type immune responses in CFS compared to controls. In contrast, levels of IFN- γ , IL-2 and IL-10-producing cells were similar in both study groups. Non-stimulated cultures revealed significantly higher levels of T cells producing IFN- γ or IL-4 in CFS patients. Concluding, we show evidence for an effector memory cell bias towards type 2 responsiveness in patients with CFS, as well as ongoing type 0 immune activation in unstimulated cultures of peripheral blood cells.

Shin H.-Y., An N.-H., Cha Y.-J., Shin E.-J., Shin T.-Y., Baek S.-H., Kim C.-H., Lyu Y.-S., Lee E.-J., Kim H.-M.

Effect of Kuibitang on lipopolysaccharide-induced cytokine production in peripheral blood mononuclear cells of chronic fatigue syndrome patients

2004 Journal of Ethnopharmacology 90 (02-Mar); 253 – 259

<http://www.scopus.com/inward/record.url?eid=2-s2.0-10744227581&partnerID=40>

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Kuibitang (KBT) is clinically used to treat patients suffering from chronic fatigue syndrome (CFS) in South Korea. However, its effect has not been investigated experimentally. Recent reports have shown that CFS patients display an altered cytokine production. We examined the effect of KBT on lipopolysaccharide (LPS)-induced various cytokines production in peripheral blood mononuclear cells (PBMC) of CFS patients and healthy controls. KBT (1mg/ml) significantly inhibited LPS-induced tumor necrosis factor- α , interleukin-10, and transforming growth factor- β 1 production in PBMC of CFS patients. However, LPS-induced interferon- γ production was significantly increased by KBT (0.01mg/ml). These results provide evidence of a novel activity of the KBT that regulate cytokines production related with CFS. © 2003 Elsevier Ireland Ltd. All rights reserved.

Sackner M.A., Gummels E.M., Adams J.A.

Say NO to fibromyalgia and chronic fatigue syndrome: An alternative and complementary therapy to aerobic exercise

2004 Medical Hypotheses 63 (1); 118 – 123

<http://www.scopus.com/inward/record.url?eid=2-s2.0-3042808131&partnerID=40>

Mt. Sinai Med. Ctr. of Greater Miami, Div. Pulmon. Dis. Critical Care Med., Department of Neonatology, Miami Beach, FL 33140, United States

Increased shear stress to the endothelium increases activity of endothelial nitric oxide synthase (eNOS) with subsequent release of small quantities (nMol) of nitric oxide (NO) into the circulation. It occurs during moderate aerobic exercise mostly as a result of laminar shear stress and with whole body, periodic acceleration as a result of pulsatile shear stress. The latter is administered by means of a new, non-invasive, passive exercise device. Moderate exercise has long been known to alleviate the symptoms of fibromyalgia and chronic fatigue syndrome and in the current study, whole body, periodic acceleration did as well. Since NO through action of eNOS has potent anti-inflammatory properties mainly by suppressing nuclear factor κ B activity, it is hypothesized that both diseases

have chronic inflammation as their basis. Whole body periodic acceleration can be applied separately or supplementary to aerobic exercise in the treatment of fibromyalgia and chronic fatigue syndrome. © 2004 Elsevier Ltd. All rights reserved.

Racciatti D., Dalessandro M., Delle Donne L., Falasca K., Zingariello P., Paganelli R., Pizzigallo E., Vecchiet J.

Study of immune alterations in patients with chronic fatigue syndrome with different etiologies.

2004 International journal of immunopathology and pharmacology 17 (2 Suppl); 57 – 62

<http://www.scopus.com/inward/record.url?eid=2-s2.0-39049188844&partnerID=40>

Sections of Infectious Diseases, Department of Medicine and Sciences of Aging, Centre of Excellence on Aging, University G. D'Annunzio, Chieti, Italy.

The Chronic Fatigue Syndrome (CFS) is characterized by symptoms lasting for at least six months and accompanied by disabling fatigue. The etiology of CFS is still unclear. At the National Center for Study of the Infectious Diseases Department of the Chieti University some immune investigations were performed with the purpose of detecting markers of the disease. CD4+, CD8+, NK CD56+ and B CD19+ lymphocytes were studied in 92 male and 47 female patients and in 36 control subjects. CFS patients were divided in three groups with a post-infectious onset (PI-CFS), a non post-infectious onset (NPI-CFS) and a non post-infectious onset with associated infections (NPI-CFS + AI). Both CD4+ and CD8+ lymphocytes were reduced in the CFS patients. However, the CD4+/CD8+ ratio was increased in the CFS patients without difference between males and females. CD56+ cells of CFS patients were also reduced. In particular, blood CD56+ cells counts were significantly higher in PI-CFS patients than in the NPI-CFS subjects. These data confirm our preliminary results suggesting a key-role of a dysfunction of the immune system as a precipitating and-or perpetuating factor of the syndrome.

Itoh Y., Hamada H., Igarashi T., Kuwabara N., Imai T., Fujino O., Fukunaga Y.

A case with chronic fatigue syndrome with positive antinuclear antibody followed by postpartum thyroiditis

2004 Modern Rheumatology 14 (5); 406 – 409

<http://www.scopus.com/inward/record.url?eid=2-s2.0-8444242902&partnerID=40>

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Autoimmune fatigue syndrome (AIFS) is defined by chronic nonspecific complaints, a positive antinuclear antibody (ANA) assay, and the absence of another explanation for the complaints. Some severe cases fulfill the criteria for chronic fatigue syndrome (CFS). CFS is a syndrome characterized by disabling severe fatigue and defined by the criteria proposed by the U.S. Centers for Disease Control and Prevention. In this report, a patient with chronic fatigue syndrome and positive ANA assay was described as having developed postpartum thyroiditis 5 years after the onset. Subchemical hypothyroidism is characterized by clinical hypothyroidism not meeting biochemical criteria but showing evidence of thyroid autoimmunity. The relation between AIFS and subchemical hypothyroidism is discussed. © Japan College of Rheumatology and Springer-Verlag Tokyo 2004.

Famularo G., De Simone C., Trinchieri V., Mosca L.

Carnitines and its congeners: A metabolic pathway to the regulation of immune response and inflammation

2004 Annals of the New York Academy of Sciences 1033; 132 – 138

<http://www.scopus.com/inward/record.url?eid=2-s2.0-10644296222&partnerID=40>

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Carnitine and its congeners may regulate the immune networks, and their influence on functions of immune cells predominantly or exclusively relies on carnitine-dependent energy production from fatty acids. A reduced pool of carnitines has been demonstrated in either serum or tissues, or both, from patients with a wide spectrum of disorders characterized by unregulated or impaired immune responses ranging from sepsis syndrome to systemic sclerosis, infection with human immunodeficiency virus, and chronic fatigue syndrome. Furthermore, experimental studies have consistently reported that the deranged immune responses and the less efficient inflammation towards infectious organisms associated with aging may be enhanced or modulated by treatment with carnitines. There is also evidence that carnitine deprivation could adversely affect the course of the sepsis syndrome, at least in experimental models, and preliminary studies suggest that carnitine deficiency is ultimately implicated in the pathophysiology of endotoxin-mediated multiple organ failure. Several data indicate that carnitine deficiency is a contributing factor to the progression of infection with human immunodeficiency virus, and carnitine therapy in those patients could counteract the unregulated process of lymphocyte apoptosis and improve CD4 counts. Some case reports have suggested the use of carnitine for the treatment of the severe lactic acidosis that complicates in some patients the use of reverse transcriptase inhibitors.

Zuckerman A.J.

Safety of hepatitis B vaccines

2004 Travel Medicine and Infectious Disease 2 (2); 81 – 84

<http://www.scopus.com/inward/record.url?eid=2-s2.0-3543142317&partnerID=40>

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Although concerns about vaccine safety have increased, true adverse reactions associated with hepatitis B vaccines are few, apart from minor symptoms at the site of injection and occasionally systemic reactions. There is no evidence of an association with hepatitis B vaccination and Sudden Infant Death Syndrome, Multiple Sclerosis and the Chronic Fatigue Syndrome. Hepatitis B vaccines are safe and essential for the prevention of this important and common infection. © 2004 Elsevier Ltd. All rights reserved.

Zachrisson O., Colque-Navarro P., Gottfries C.G., Regland B., Mollby R.

Immune modulation with a staphylococcal preparation in fibromyalgia/ chronic fatigue syndrome: Relation between antibody levels and clinical improvement

2004 European Journal of Clinical Microbiology and Infectious Diseases 23 (2); 98 – 105

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1642330292&partnerID=40>

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The aims of this study were to evaluate the serological response to treatment with staphylococcal vaccine in fibromyalgia/chronic fatigue syndrome patients and to explore the relationship between serological response and clinical effect. Twenty-eight patients, half of whom served as controls, were recruited from a 6-month randomised trial in which repeated administration of the staphylococcal toxoid vaccine Staphypan Berna (Berna Biotech, Switzerland) was tested against placebo. Antibody status against extracellular toxins/enzymes, cell-wall components, and enterotoxins was evaluated at baseline and at endpoint. The clinical response to treatment was recorded in rating scales. In the group receiving active treatment, significant serological changes were recorded, whereas no significant changes were found in controls. Treatment led to a significantly increased capacity of serum to neutralise alpha-toxin and a significant increase in serum IgG to alpha-toxin and lipase. Furthermore, the increase in these parameters combined paralleled the improvement in clinical outcome. Thus, the greater the serological response, the greater was the clinical effect. In conclusion, this explorative study has shown that repeated administration of the Staphypan Berna vaccine in patients with fibromyalgia/chronic fatigue syndrome causes a serological response to several staphylococcal antigens, particularly to certain extracellular toxins and enzymes. The results further show that this response is related to the clinical outcome of treatment. © Springer-Verlag 2004.

White P.D., Thomas J.M., Sullivan P.F., Buchwald D.
The nosology of sub-acute and chronic fatigue syndromes that follow infectious mononucleosis
2004 Psychological Medicine 34 (3); 499 - 507
<http://www.scopus.com/inward/record.url?eid=2-s2.0-2342442206&partnerID=40>

Department of Psychological Medicine, Barts London/Queen Mary Sch. of Med., University of London, London, United Kingdom; Department of Medicine, University of Washington, Seattle, WA, United States; Department of Genetics, Univ. North Carolina at Chapel Hill, Chapel Hill, NC, United States; Department of Psychological Medicine, St Bartholomew's Hospital, London EC1A 7BE, United Kingdom

Background. A previous principal components analysis of symptoms occurring after infectious mononucleosis suggested that a discrete fatigue syndrome occurs, which is independent of psychiatric disorder. This work has not been replicated and no latent class analysis of subjects has been published. Method. We prospectively examined a cohort of 150 American primary care patients 2 and 6 months after the onset of corroborated infectious mononucleosis. A subset of 50 subjects was studied 4 years after onset. We performed principal components analyses of both psychological and somatic symptoms and latent class analyses of subjects. Results. Principal components analyses consistently delineated two fatigue factors at 2 and 6 months and one fatigue factor at 4 years. These factors were separate from a mixed anxiety and depressive factor. A four-class solution for the latent class analyses consisted of most subjects with few symptoms, a few with many symptoms, a group with predominantly mood symptoms and some subjects with fatigue symptoms. Conclusions. The symptoms of the principal factors with fatigue were similar to those previously described. Both the factors and classes were independent of an equally delineated mood factor and class. These results support the existence of two discrete chronic fatigue syndromes after infectious mononucleosis, one of which is still demonstrable 4 years after onset. © 2004 Cambridge University Press.

Nicolson G.L., Gan R., Haier J.
Evidence for Brucella spp. and Mycoplasma spp. co-infections in blood of chronic fatigue syndrome patients
2004 Journal of Chronic Fatigue Syndrome 12 (2); 5 - 17

<http://www.scopus.com/inward/record.url?eid=2-s2.0-22844452824&partnerID=40>

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We examined the blood of 94 North American Chronic Fatigue Syndrome (CFS) patients using forensic polymerase chain reaction and found that a subset (10.6%) of CFS patients show evidence of *Brucella* spp. infections compared to one of 70 control subjects (Odds Ratio = 8.2; 95% Confidence Limits (CL) 1-66; $P < .01$). Rural patients showed a higher incidence of *Brucella* spp. infections over urban patients (OR = 5.5, 95% CL 1.3-23.5, $P < .02$). Since CFS patients also have a high prevalence of one of four *Mycoplasma* species and sometimes show evidence of infections with *Chlamydia pneumoniae*, we examined *Brucella*-positive patients for other bacterial infections. Previously we found that 8% of the CFS patients showed evidence of *C. pneumoniae* and about 50% show evidence of *Mycoplasma* spp. infections. Since the presence of one or more chronic systemic infections may predispose patients to other infections, we examined the prevalence of *C. pneumoniae* and *Mycoplasma* spp. infections in *Brucella*-positive patients. We found only one *Brucella*-positive patient with *C. pneumoniae* and four other patients with evidence of *Mycoplasma* spp., suggesting that such bacterial infections occur independently in CFS patients. Control subjects ($N = 70$) had low rates of *Brucella* spp. (1.4%), *Mycoplasma* spp. (7.2%) or *C. pneumoniae* (1.4%) infections, and there were no co-infections in control subjects. The results indicate that a subset of CFS patients show evidence of infection with *Brucella* spp., and some of these patients also have other bacterial infections. © 2004 by The Haworth Press, Inc. All rights reserved.

Mears C.J., Taylor R.R., Jordan K.M., Binns H.J.

Sociodemographic and symptom correlates of fatigue in an adolescent primary care sample

2004 *Journal of Adolescent Health* 35 (6)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-9644272436&partnerID=40>

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Purpose To describe the prevalence of prolonged fatigue, chronic fatigue syndrome (CFS)-like illness, and associated symptom patterns in adolescents attending primary care. **Methods** The design was cross-sectional. A questionnaire designed by the authors assessing fatigue and associated symptoms was administered to 901 adolescents (aged 11-18 years) attending 12 primary care clinics in the Chicago area. Prevalence rates for prolonged fatigue and CFS-like illness were calculated. Univariate comparisons involving sociodemographic data and fatigue severity were made between adolescents with and without prolonged fatigue, and sociodemographic and symptom predictors of prolonged fatigue were identified using logistic regression analysis. **Results** Prolonged fatigue (≥ 1 month) occurred at a rate of 8.0% and CFS-like illness occurred at a rate of 4.4%. Adolescents with prolonged fatigue were significantly older and also reported greater fatigue severity than those without fatigue. Findings from logistic regression indicated that, in addition to increasing age, headaches, muscle pains, fever, and fatigue made worse by exercise were significantly associated with prolonged fatigue. **Conclusions** Abnormal fatigue is a disabling and prevalent condition in adolescents in primary care. It is associated with a number of additional symptoms, many of which may have viral origins. © Society for Adolescent Medicine, 2004.

Lerner A.M., Beqaj S.H., Deeter R.G., Fitzgerald J.T.

IgM serum antibodies to Epstein-Barr virus are uniquely present in a subset of patients with the chronic fatigue syndrome

2004 In Vivo 18 (2); 101 - 106

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1842841760&partnerID=40>

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Background: A unique subset of patients with chronic fatigue syndrome (CFS) and IgM serum antibodies to cytomegalovirus (HCMV) non-structural gene products p52 and CM2 (UL 44 and UL 57) has been described. Patients and Methods: Fifty-eight CFS patients and 68 non-CFS matched controls were studied. Serum antibodies to EBV viral capsid antigen (VCA) IgM and EBV Early Antigen, diffuse (EA, D) as well HVCMV(V), IgM and IgG; VP (sucrose, density purified V); p52 and CM2 IgM serum antibodies were assayed. Results: Mean age of CFS patients was 44 years (75% women). Control patients were 9 years older (73% women). Serum EBV VCA IgM positive antibody titers were identified in 33 CFS patients (Group A subset EBV VCA IgM 62.3 ± 8.3 , neg. < 20), but were not present in other CFS patients, (Group B subset EBV VCA IgM 6.8 ± 0.7) controls ($p < 0.0001$). EBV VCA IgM titers remained positive in CFS patients from Group A for 24-42 months. Conclusion: Serum antibody to EBV VCA IgM may be a specific diagnostic test for a second subset of CFS patients.

Kennedy G., Spence V., Underwood C., Belch J.J.F.

Increased neutrophil apoptosis in chronic fatigue syndrome

2004 Journal of Clinical Pathology 57 (8); 891 – 893

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4043125293&partnerID=40>

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Background/Aims: Many patients with chronic fatigue syndrome (CFS) have symptoms that are consistent with an underlying viral or toxic illness. Because increased neutrophil apoptosis occurs in patients with infection, this study examined whether this phenomenon also occurs in patients with CFS. Methods: Apoptosis was assessed in patients with CFS in conjunction with concentrations of the anti-inflammatory cytokine, transforming growth factor β_1 (TGF β_1). Results: The 47 patients with CFS had higher numbers of apoptotic neutrophils, lower numbers of viable neutrophils, increased annexin V binding, and increased expression of the death receptor, tumour necrosis factor receptor-I, on their neutrophils than did the 34 healthy controls. Patients with CFS also had raised concentrations of active TGF β_1 ($p < 0.005$). Conclusions: These findings provide new evidence that patients with CFS have an underlying detectable abnormality in their immune cells.

Chia J.K., Chia A.Y.

Ribavirin and interferon- β for the treatment of patients with chronic fatigue syndrome associated with persistent coxsackievirus B infection: A preliminary observation

2004 Journal of Applied Research 4 (2); 286 – 292

<http://www.scopus.com/inward/record.url?eid=2-s2.0-6344228464&partnerID=40>

I D Med, Torrance, CA, United States

Several studies have demonstrated elevated neutralizing antibodies to coxsackievirus B (CBV) and the presence of enteroviral RNA in peripheral blood in a subset of patients with chronic fatigue syndrome (CFS). Of 10 patients with stable, persistently high titer of neutralizing antibody against CBV-3 and CBV-5 were treated with ribavirin for 4 months, and 5 patients were subsequently treated with interferon/ribavirin for 2 to 6 months. Seven of 10 patients had significant improvement of fatigue and viral symptoms during ribavirin therapy, along with more than a fourfold decrease of neutralizing antibody. Most patients relapsed within 1 to 2 weeks of medication discontinuation, with subsequent rebound of neutralizing antibody to pre-treatment baseline and had detectable enteroviral RNA in blood leukocytes. Combination therapy resulted in the disappearance of enteroviral RNA, decrease in neutralizing antibody in 4 of 5 patients, and significant, short-term symptomatic improvement following completion of therapy in 4 of 5 patients. Relapse occurred about 4 months later in most patients along with rebound of neutralizing antibody titer and reappearance of enteroviral RNA. Antiviral therapy may be beneficial in a subset of CFS patients with persistent CBV infection.

Shapiro J.S.

Does varicella-zoster virus infection of the peripheral ganglia cause Chronic Fatigue Syndrome?

Medical Hypotheses

<http://www.scopus.com/inward/record.url?eid=2-s2.0-66449134622&partnerID=40>

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This article posits that infection of the peripheral ganglia causes at least some cases of Chronic Fatigue Syndrome (CFS), with a neurotropic herpesvirus, particularly varicella-zoster virus (VZV), as the most likely cause of the infection. Virtually all CFS symptoms could be produced by an infection of the peripheral ganglia, with infection of the autonomic ganglia causing fatigue, postural hypotension, and sleep disturbances, and infection of the sensory ganglia causing sensory symptoms such as chronic pain. Furthermore, infections of the peripheral ganglia are known to cause long-term nerve dysfunction, which would help explain the chronic course of CFS. Herpesviruses have long been suspected as the cause of CFS; this theory has recently been supported by studies showing that administering antiherpes agents causes substantial improvement in some CFS patients. VZV is known to frequently reactivate in the peripheral ganglia of previously healthy adults and cause sudden, debilitating illness, making it a likely candidate as a cause of CFS. Moreover, many of the symptoms of CFS overlap with those of herpes zoster (shingles), with the exception that painful rash is not one of the symptoms of CFS. A model is therefore proposed in which CFS is one of the many manifestations of zoster sine herpette; that is, herpes zoster without rash. Furthermore, re-exposure to VZV in the form of chickenpox has become less common in the past few decades; without such re-exposure, immunity to VZV drops, which could explain the increased incidence of CFS. Co-infection with multiple herpesviruses is a possibility, as some CFS patients show signs of infection with other herpesviruses including Epstein-Barr, Cytomegalovirus, and HHV6. These three herpesviruses can attack immune cells, and may therefore promote neurotropic herpesvirus reactivation in the ganglia. The possibility of VZV as the causal agent in CFS has previously received almost no attention; the possibility that CFS involves infection of the peripheral ganglia has likewise been largely overlooked. This suggests that the search for a viral cause of CFS has been far from exhaustive. Several antiherpes drugs are available, as is a vaccine for VZV; more research into such agents as possible treatments for CFS is urgently needed. © 2009.

Neuroendocrinology

Roberts A.D.L., Papadopoulos A.S., Wessely S., Chalder T., Cleare A.J.

Salivary cortisol output before and after cognitive behavioural therapy for chronic fatigue syndrome

2009 Journal of Affective Disorders 115 (01-Feb); 280 – 286

<http://www.scopus.com/inward/record.url?eid=2-s2.0-62649126197&partnerID=40>

King's College London, Institute of Psychiatry, Department of Psychological Medicine, De Crespigny Park, London, SE5 8AF, United Kingdom; Chronic Fatigue Syndrome Research and Treatment Unit, Maudsley Hospital, Denmark Hill, London, United Kingdom; National Affective Disorders Unit, Maudsley and Bethlem Royal Hospitals, Denmark Hill, London, United Kingdom

Background: There is evidence that patients with chronic fatigue syndrome (CFS) have mild hypocortisolism. One theory about the aetiology of this hypocortisolism is that it occurs late in the course of CFS via factors such as inactivity, sleep disturbance, chronic stress and deconditioning. We aimed to determine whether therapy aimed at reversing these factors - cognitive behavioural therapy for CFS - could increase cortisol output in CFS. **Methods:** We measured diurnal salivary cortisol output between 0800 and 2000h before and after 15 sessions (or 6 months) of CBT in 41 patients with CDC-defined CFS attending a specialist, tertiary outpatient clinic. **Results:** There was a significant clinical response to CBT, and a significant rise in salivary cortisol output after CBT. **Limitations:** We were unable to control for the passage of time using a non-treated CFS group. **Conclusions:** Hypocortisolism in CFS is potentially reversible by CBT. Given previous suggestions that lowered cortisol may be a maintaining factor in CFS, CBT offers a potential way to address this. © 2008 Elsevier B.V. All rights reserved.

Roberts A.D.L., Charler M.-L., Papadopoulos A., Wessely S., Chalder T., Cleare A.J.

Does hypocortisolism predict a poor response to cognitive behavioural therapy in chronic fatigue syndrome?

2009 Psychological Medicine 1 (8)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650353906&partnerID=40>

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BACKGROUND: There is evidence that patients with chronic fatigue syndrome (CFS) have mild hypocortisolism. The clinical significance of this is unclear. We aimed to determine whether hypocortisolism exerted any effect on the response of CFS to cognitive behavioural therapy (CBT). **METHOD:** We measured 24-h urinary free cortisol (UFC) in 84 patients with Centers for Disease Control and Prevention (CDC)-defined CFS (of whom 64 were free from psychotropic medication) who then received CBT in a specialist, tertiary out-patient clinic as part of their usual clinical care. We also measured salivary cortisol output from 0800 to 2000 h in a subsample of 56 psychotropic medication-free patients. **RESULTS:** Overall, 39% of patients responded to CBT after 6 months of treatment. Lower 24-h UFC output was associated with a poorer response to CBT but only in psychotropic medication-free patients. A flattened diurnal profile of salivary cortisol was also associated with a poor response to CBT. **CONCLUSIONS:** Low cortisol is of clinical relevance in CFS, as it is associated with a poorer response to CBT. Hypocortisolism could be one of several maintaining factors that interact in the persistence of CFS.

Papadopoulos A., Ebrecht M., Roberts A.D.L., Poon L., Rohleder N., Cleare A.J.
Glucocorticoid receptor mediated negative feedback in chronic fatigue syndrome using the low dose (0.5 mg) dexamethasone suppression test

2009 Journal of Affective Disorders 112(01-Mar); 289 – 294

<http://www.scopus.com/inward/record.url?eid=2-s2.0-56549121563&partnerID=40>

King's College London, Institute of Psychiatry, Section of Neurobiology of Mood Disorders, London, SE5 8AF, United Kingdom; National Affective Disorders Unit, Bethlem Royal and Maudsley Hospitals, London, United Kingdom; King's College London, Department of Psychology, Guy's, Kings and St Thomas' School of Medicine, London SE1 9RT, United Kingdom; Chronic Fatigue Syndrome Unit, King's College Hospital, London, United Kingdom; Biopsychology Unit, Technical University of Dresden, Dresden, Germany

Background: Chronic fatigue syndrome (CFS) is associated with hypocortisolism, but it is not yet clear the extent to which enhanced negative feedback may underlie this finding. Methods: We undertook a low-dose dexamethasone (0.5 mg) suppression test in 18 CFS patients and 20 matched, healthy controls. We measured salivary cortisol levels at 0800 h, 1200 h, 1600 h and 2000 h before and after the administration of 0.5 mg of dexamethasone. Results: Basal cortisol output was raised in this group of CFS patients compared to controls. Overall, the percentage suppression following dexamethasone administration was no different between CFS (mean \pm sem: 80.4 \pm 4.4%) and controls (76.2 \pm 4.9 %). However, the sub-group of patients with CFS and comorbid depression (n = 9) showed a significant hypersuppression of salivary cortisol in response to dexamethasone (89.0 \pm 1.9%; p < 0.05 v controls). Limitations: The sub-group analysis was on small numbers and should be considered preliminary. Dexamethasone probes only glucocorticoid mediated negative feedback but does not probe mineralocorticoid feedback, the other main physiological feedback mechanism. Conclusion: We found partial support for the hypothesis of enhanced negative feedback in CFS but only in patients with comorbid depression and also in the context of a sample of patients with elevated basal cortisol levels, which is an atypical finding in the literature. © 2008 Elsevier B.V. All rights reserved.

Miwa K., Fujita M.
Increased oxidative stress suggested by low serum vitamin E concentrations in patients with chronic fatigue syndrome

2009 International Journal of Cardiology 136 (2); 238 – 239

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650727423&partnerID=40>

Department of Internal Medicine, Nanto Home and Regional Medical Center, 577 Matsubara, Nanto, Toyama, 939-1518, Japan; Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

Serum $\hat{\pm}$ -tocopherol concentrations were determined in 50 patients with chronic fatigue syndrome (CFS) and 40 control subjects (Control). Prevalence of each or any coronary risk factor was not significantly different between CFS and Control. CFS had significantly lower $\hat{\pm}$ -tocopherol concentrations than Control. The concentrations were significantly lower in the subjects with any coronary risk factors than those without in CFS as well as Control. Even among the subjects with any coronary risk factors and also among those without, CFS had significantly lower $\hat{\pm}$ -tocopherol concentrations than Control. In conclusion, CFS had significantly lower $\hat{\pm}$ -tocopherol concentrations irrespective of coronary risk factors than Control, suggesting the presence of increased oxidative stress in CFS. © 2008 Elsevier Ireland Ltd. All rights reserved.

Heim C., Nater U.M., Maloney E., Boneva R., Jones J.F., Reeves W.C.
Childhood trauma and risk for chronic fatigue syndrome Association with Neuroendocrine Dysfunction

2009 Archives of General Psychiatry 66 (1); 72 – 80

<http://www.scopus.com/inward/record.url?eid=2-s2.0-58149520651&partnerID=40>

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Context: Childhood trauma appears to be a potent risk factor for chronic fatigue syndrome (CFS). Evidence from developmental neuroscience suggests that early experience programs the development of regulatory systems that are implicated in the pathophysiology of CFS, including the hypothalamic-pituitary-adrenal axis. However, the contribution of childhood trauma to neuroendocrine dysfunction in CFS remains obscure. Objectives: To replicate findings on the relationship between childhood trauma and risk for CFS and to evaluate the association between childhood trauma and neuroendocrine dysfunction in CFS. Design, Setting, and Participants: A case-control study of 113 persons with CFS and 124 well control subjects identified from a general population sample of 19 381 adult residents of Georgia. Main Outcome Measures: Self-reported childhood trauma (sexual, physical, and emotional abuse; emotional and physical neglect), psychopathology (depression, anxiety, and posttraumatic stress disorder), and salivary cortisol response to awakening. Results: Individuals with CFS reported significantly higher levels of childhood trauma and psychopathological symptoms than control subjects. Exposure to childhood trauma was associated with a 6-fold increased risk of CFS. Sexual abuse, emotional abuse, and emotional neglect were most effective in discriminating CFS cases from controls. There was a graded relationship between exposure level and CFS risk. The risk of CFS conveyed by childhood trauma further increased with the presence of posttraumatic stress disorder symptoms. Only individuals with CFS and with childhood trauma exposure, but not individuals with CFS without exposure, exhibited decreased salivary cortisol concentrations after awakening compared with control subjects. Conclusions: Our results confirm childhood trauma as an important risk factor of CFS. In addition, neuroendocrine dysfunction, a hallmark feature of CFS, appears to be associated with childhood trauma. This possibly reflects a biological correlate of vulnerability due to early developmental insults. Our findings are critical to inform pathophysiological research and to devise targets for the prevention of CFS. © 2009 American Medical Association.

Evans K.M., Flanagan D.E., Wilkin T.J.
Chronic fatigue: Is it endocrinology?

2009 Clinical Medicine, Journal of the Royal College of Physicians of London 9 (1); 34 – 38

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Fatigue and stress-related illnesses often become diagnoses of exclusion after extensive investigation. 'Tired all the time' is a frequent reason for referral to the endocrine clinic, the implicit question being - is there a subtle endocrine pathology contributing to the patient's symptoms? Often initial assessment suggests not but there are no clear data to address the question of whether overt pathology will develop in the future. This study observed outcomes after five years in 101 consecutive and unselected referrals to secondary care for 'fatigue?cause', where initial assessment did not suggest treatable endocrine pathology. The findings suggest that the clinical diagnosis of fatigue, based on history and tests to exclude anaemia, hypothyroidism and diabetes, is secure: these patients do not subsequently demonstrate excess morbidity and mortality, and their presenting symptoms are not early features of significant endocrine pathology. © Royal College of Physicians, 2009. All rights reserved.

Ben-Zvi A., Vernon S.D., Broderick G.

Model-based therapeutic correction of hypothalamic-pituitary-adrenal axis dysfunction

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The hypothalamic-pituitary-adrenal (HPA) axis is a major system maintaining body homeostasis by regulating the neuroendocrine and sympathetic nervous systems as well modulating immune function. Recent work has shown that the complex dynamics of this system accommodate several stable steady states, one of which corresponds to the hypocortisol state observed in patients with chronic fatigue syndrome (CFS). At present these dynamics are not formally considered in the development of treatment strategies. Here we use model-based predictive control (MPC) methodology to estimate robust treatment courses for displacing the HPA axis from an abnormal hypocortisol steady state back to a healthy cortisol level. This approach was applied to a recent model of HPA axis dynamics incorporating glucocorticoid receptor kinetics. A candidate treatment that displays robust properties in the face of significant biological variability and measurement uncertainty requires that cortisol be further suppressed for a short period until adrenocorticotrophic hormone levels exceed 30% of baseline. Treatment may then be discontinued, and the HPA axis will naturally progress to a stable attractor defined by normal hormone levels. Suppression of biologically available cortisol may be achieved through the use of binding proteins such as CBG and certain metabolizing enzymes, thus offering possible avenues for deployment in a clinical setting. Treatment strategies can therefore be designed that maximally exploit system dynamics to provide a robust response to treatment and ensure a positive outcome over a wide range of conditions. Perhaps most importantly, a treatment course involving further reduction in cortisol, even transient, is quite counterintuitive and challenges the conventional strategy of supplementing cortisol levels, an approach based on steady-state reasoning. © 2009 Ben-Zvi et al.

Van Den Eede F., Moorkens G., Hulstijn W., Van Houdenhove B., Cosyns P., Sabbe B.G.C., Claes S.J.
Combined dexamethasone/corticotropin-releasing factor test in chronic fatigue syndrome

2008 Psychological Medicine 38 (7); 963 - 970

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Background. Studies of hypothalamic-pituitary-adrenal (HPA) axis function in chronic fatigue syndrome (CFS) point to hypofunction, although there are negative reports. Suggested mechanisms include a reduced hypothalamic or supra-hypothalamic stimulus to the HPA axis and enhanced sensitivity to the negative feedback of glucocorticoids. The aim of the current study was to investigate HPA axis function in CFS with the dexamethasone/corticotropin-releasing factor (Dex/CRF) test, in analogy with research in affective disorders. **Method.** Thirty-four well-characterized female CFS patients and 25 healthy control subjects participated in the low-dose Dex/CRF test. Current major depressive episode was an exclusion criterion. History of early-life stress (ELS) was assessed with the Structured Trauma Interview. **Results.** Salivary cortisol responses after 0.5 mg Dex were lower in CFS patients than in controls (before 100 μ g CRF, $p=0.038$; after 100 μ g CRF, $p=0.015$). A secondary analysis revealed an influence of early-life

stress and of oestrogen intake. After removal of the 10 participants who were taking an oral oestrogen, patients without a history of ELS showed lower cortisol responses than patients with ELS and controls (before CRF, $p=0.005$; after CRF, $p=0.008$). Conclusions. CFS is globally associated with reduced cortisol responses in the combined low-dose Dex/CRF test, but this effect is only clearly present in CFS patients without a history of ELS. This study provides further support for an enhanced glucocorticoid negative feedback and/or a reduced central HPA axis drive in CFS. Furthermore, it demonstrates that ELS is an important variable to consider in CFS research. Copyright © 2007 Cambridge University Press.

Torres-Harding S., Sorenson M., Jason L., Reynolds N., Brown M., Maher K., Fletcher M.A.
The associations between basal salivary cortisol and illness symptomatology in chronic fatigue syndrome

2008 Journal of Applied Biobehavioral Research 13 (3); 157 – 180

<http://www.scopus.com/inward/record.url?eid=2-s2.0-57349173514&partnerID=40>

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Hypocortisolism has been reported in chronic fatigue syndrome (CFS), with the significance of this finding to disease etiology unclear. This study examined cortisol levels and their relationships with symptoms in a group of 108 individuals with CFS. CFS symptoms examined included fatigue, pain, sleep difficulties, neurocognitive functioning, and psychiatric status. Alterations in cortisol levels were examined by calculation of mean daily cortisol, and temporal variation in cortisol function was examined by means of a regression slope. Additionally, deviation from expected cortisol diurnal pattern was determined via clinical judgment. Results indicated that fatigue and pain were associated with salivary cortisol levels. In particular, variance from the expected pattern of cortisol was associated with increased levels of fatigue. The implications of these findings are discussed. © 2008 Wiley Periodicals, Inc.

Nater U.M., Youngblood L.S., Jones J.F., Unger E.R., Miller A.H., Reeves W.C., Heim C.
Alterations in diurnal salivary cortisol rhythm in a population-based sample of cases with chronic fatigue syndrome

2008 Psychosomatic Medicine 70 (3); 298 - 305

<http://www.scopus.com/inward/record.url?eid=2-s2.0-42149099885&partnerID=40>

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OBJECTIVE: To examine diurnal salivary cortisol rhythms and plasma IL-6 concentrations in persons with chronic fatigue syndrome (CFS), persons not fulfilling a diagnosis of CFS (we term them cases with insufficient symptoms or fatigue, ISF) and nonfatigued controls (NF). Previous studies of CFS patients have implicated the hypothalamic-pituitary-adrenal axis and the immune system in the pathophysiology of CFS, although results have been equivocal. **METHODS:** Twenty-eight people with CFS, 35 persons with ISF, and 39 NF identified from the general population of Wichita, Kansas, were admitted to a research ward for 2 days. Saliva was collected immediately on awakening (6:30 am), at 08:00 am, 12 noon, 4:00 pm, 8:00 pm and at bedtime (10:00 pm) and plasma was obtained at 7:30 am. Salivary cortisol concentrations were assessed using radioimmunoassay, and plasma IL-6 was measured using sandwich enzyme-linked immunosorbent assay. **RESULTS:** People with CFS demonstrated lower salivary cortisol concentrations in the morning and higher salivary cortisol concentrations in the evening compared with both ISF and NF groups indicating a flattening of the

diurnal cortisol profile. Mean plasma IL-6 concentrations were highest in CFS compared with the other groups, although these differences were no longer significant after controlling for BMI. Attenuated decline of salivary cortisol concentrations across the day and IL-6 concentration were associated with fatigue symptoms in CFS. CONCLUSIONS: These results suggest an altered diurnal cortisol rhythm and IL-6 concentrations in CFS cases identified from a population-based sample. Copyright © 2008 by American Psychosomatic Society.

Nater U.M., Maloney E., Boneva R.S., Gurbaxani B.M., Lin J.-M., Jones J.F., Reeves W.C., Heim C.
Attenuated morning salivary cortisol concentrations in a population-based study of persons with chronic fatigue syndrome and well controls

2008 Journal of Clinical Endocrinology and Metabolism 93 (3); 703 – 709

<http://www.scopus.com/inward/record.url?eid=2-s2.0-40849106397&partnerID=40>

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Context: A substantial body of research on the pathophysiology of chronic fatigue syndrome (CFS) has focused on hypothalamic-pituitary-adrenal axis dysregulation. The cortisol awakening response has received particular attention as a marker of hypothalamic-pituitary-adrenal axis dysregulation. Objective: The objective of the current study was to evaluate morning salivary cortisol profiles in persons with CFS and well controls identified from the general population. Design and Setting: We conducted a case-control study at an outpatient research clinic. Cases and Other Participants: We screened a sample of 19,381 residents of Georgia and identified those with CFS and a matched sample of well controls. Seventy-five medication-free CFS cases and 110 medication-free well controls provided complete sets of saliva samples. Main Outcome Measures: We assessed free cortisol concentrations in saliva collected on a regular workday immediately upon awakening and 30 and 60 min after awakening. Results: There was a significant interaction effect, indicating different profiles of cortisol concentrations over time between groups, with the CFS group showing an attenuated morning cortisol profile. Notably, we observed a sex difference in this effect. Women with CFS exhibited significantly attenuated morning cortisol profiles compared with well women. In contrast, cortisol profiles were similar in men with CFS and male controls. Conclusions: CFS was associated with an attenuated morning cortisol response, but the effect was limited to women. Our results suggest that a sex difference in hypocortisolism may contribute to increased risk of CFS in women. Copyright © 2008 by The Endocrine Society.

Holtorf K.
Diagnosis and treatment of hypothalamic-pituitary-adrenal (HPA) axis dysfunction in patients with chronic fatigue syndrome (CFS) and fibromyalgia (FM)

2008 Journal of Chronic Fatigue Syndrome 14 (3); 59 – 88

<http://www.scopus.com/inward/record.url?eid=2-s2.0-39749108072&partnerID=40>

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There is controversy regarding the incidence and significance of hypothalamic-pituitary-adrenal (HPA) axis dysfunction in chronic fatigue syndrome (CFS) and fibromyalgia (FM). Studies that utilize central acting stimulation tests, including corticotropin-releasing hormone (CRH), insulin stress testing (IST), d-fenfluramine, ipsapirone, interleukin-6 (IL-6) and metyrapone testing, have demonstrated that HPA axis dysfunction of central origin is present in a majority of these patients.

However, ACTH stimulation tests and baseline cortisol testing lack the sensitivity to detect this central dysfunction and have resulted in controversy and confusion regarding the incidence of HPA axis dysfunction in these conditions and the appropriateness of treatment. While both CFS and FM patients are shown to have central HPA dysfunction, the dysfunction in CFS is at the pituitary-hypothalamic level while the dysfunction in FM is more related to dysfunction at the hypothalamic and supra-hypothalamic levels. Because treatment with low physiologic doses of cortisol (<15 mg) has been shown to be safe and effective and routine dynamic ACTH testing does not have adequate diagnostic sensitivity, it is reasonable to give a therapeutic trial of physiologic doses of cortisol to the majority of patients with CFS and FM, especially to those who have symptoms that are consistent with adrenal dysfunction, have low blood pressure or have baseline cortisol levels in the low or low-normal range. Copyright © by The Haworth Press, Inc. All rights reserved.

Fuite J., Vernon S.D., Broderick G.
Neuroendocrine and immune network re-modeling in chronic fatigue syndrome: An exploratory analysis

2008 Genomics 92 (6); 393 - 399

<http://www.scopus.com/inward/record.url?eid=2-s2.0-55949083343&partnerID=40>

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This work investigates the significance of changes in association patterns linking indicators of neuroendocrine and immune activity in patients with chronic fatigue syndrome (CFS). Gene sets preferentially expressed in specific immune cell isolates were integrated with neuroendocrine data from a large population-based study. Co-expression patterns linking immune cell activity with hypothalamic-pituitary-adrenal (HPA), thyroidal (HPT) and gonadal (HPG) axis status were computed using mutual information criteria. Networks in control and CFS subjects were compared globally in terms of a weighted graph edit distance. Local re-modeling of node connectivity was quantified by node degree and eigenvector centrality measures. Results indicate statistically significant differences between CFS and control networks determined mainly by re-modeling around pituitary and thyroid nodes as well as an emergent immune sub-network. Findings align with known mechanisms of chronic inflammation and support possible immune-mediated loss of thyroid function in CFS exacerbated by blunted HPA axis responsiveness. © 2008 Elsevier Inc. All rights reserved.

Chen R., Moriya J., Yamakawa J.-I., Takahashi T., Li Q., Morimoto S., Iwai K., Sumino H., Yamaguchi N., Kanda T.
Brain atrophy in a murine model of chronic fatigue syndrome and beneficial effect of Hochu-ekki-to (TJ-41)

2008 Neurochemical Research 33 (9); 1759 – 1767

<http://www.scopus.com/inward/record.url?eid=2-s2.0-48349143538&partnerID=40>

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Brain-derived neurotrophic factor (BDNF) is associated with the main symptoms of chronic fatigue syndrome (CFS) and neuron apoptosis. Nevertheless, no study has been performed directly to explore the relationship between CFS, BDNF and neuron apoptosis. We induced a CFS model by six

injections of killed *Brucella abortus* antigen in BALB/c mice and treated them with Hochu-ekki-to (TJ-41). Daily running activity, body weight (BW), ratio of cerebral weight to BW (CW/BW) and expression levels of BDNF and Bcl-2 mRNA in the hippocampus were determined. The daily activity and CW/BW decreased significantly in the CFS model. BDNF and Bcl-2 mRNA expression levels in the hippocampus were suppressed in the CFS model and TJ-41 treated mice, while no significant difference was found between them. We improved a murine model to investigate the relationship between CFS and brain dysfunction. In this model, reduced daily activity might have been associated with decreased hippocampal BDNF mRNA expression, hippocampal apoptosis and brain atrophy. TJ-41 increased the daily running activity of the model, which was independent of brain recovery. © 2008 Springer Science+Business Media, LLC.

Tjorve E., Tjorve K.M.C., Olsen J.O., Senum R., Oftebro H.

On commonness and rarity of thyroid hormone resistance: A discussion based on mechanisms of reduced sensitivity in peripheral tissues

2007 Medical Hypotheses 69 (4); 913 - 921

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34547852280&partnerID=40>

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Reduced sensitivity to thyroid hormone (TH) in peripheral tissues can occur as defects in TH transport into the cell, intracellular TH metabolism, cytosolic mechanisms, TH entry into the nucleus, thyroxin receptors (TRs) and receptor binding, transcription and post-transcriptional mechanisms. Current literature reveals an extensive list of mutations, drugs, toxins, metabolites and autoimmune antibodies that may impair TH action in the cell, but such impairment may not be picked up by assays of TH and TSH in blood plasma. Substances may induce tissue specific resistance to thyroid hormone (RTH), e.g. by affecting numbers of different TR isoforms. Recent literature also indicates mechanisms by which different conditions, for example, chronic fatigue syndrome (CFS), chronic renal failure (CRF) and nonthyroidal illness, can be accompanied by acquired RTH caused by inhibition of TH metabolism, cell uptake, TR binding and transcription. This prompts us to reassess commonness and rarity of congenital vs. acquired RTH. We hypothesise that observed clinical symptoms of hypothyroidism in chemically euthyroid patients are typically caused by changes in hormonal systems, autoimmune antibodies, metabolites or other substances in the body, leading to reduced sensitivity to TH in peripheral tissues. These changes may be a by-product of other processes and a reversible biological response in the body, and may also result in chronic acquired RTH. Antibodies may prove to be the most common cause of chronic reduction in TH sensitivity. It is argued that the acquired form of RTH, caused by endogenous and exogenous sources, may indeed be more common than the congenital, as in insulin resistance. If acquired RTH exists, then it may not be picked up by blood assays of TH and TSH. An appropriate test to assess TH action in peripheral tissues is therefore greatly desired. © 2007 Elsevier Ltd. All rights reserved.

The G.K.H., Bleijenberg G., van der Meer J.W.M.

The effect of acclidyne in chronic fatigue syndrome: A randomized controlled trial

2007 PLoS Clinical Trials 2 (5)

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Objectives: It is unclear whether insulin-like growth factor (IGF) function is involved in the pathophysiology of chronic fatigue syndrome (CFS). Unpublished data and reports in patient organization newsletters suggest that Acclidyne, a food supplement, could be effective in the treatment of CFS by increasing biologically active IGF1 levels. Here we aimed to measure the IGF1

and IGF binding protein (IGFBP) 3 status of CFS patients compared to age- and gender-matched neighborhood controls, and to assess the effect of Acclidyne on fatigue severity, functional impairment, and biologically active IGF1 level (IGFBP3/IGF1 ratio). Design: A randomized, placebo-controlled, double-blind clinical trial. Setting: Radboud University Nijmegen Medical Centre, The Netherlands. Participants: Fifty-seven adult patients who fulfilled the US Centers for Disease Control and Prevention criteria for CFS. IGF status of 22 CFS patients was compared to that of 22 healthy age- and gender-matched neighborhood control individuals. Intervention: Acclidyne or placebo for 14 wk. Outcome measures: Outcomes were fatigue severity (Checklist Individual Strength, subscale fatigue severity [CIS-fatigue]), functional impairment (Sickness Impact Profile-8 [SIP-8]), and biologically active IGF1 serum concentrations. Analyses were on an intention-to-treat basis. Results: There was no difference in IGF status in 22 CFS patients compared to healthy age- and gender-matched control individuals. Treatment with Acclidyne did not result in significant differences compared with the placebo group on any of the outcome measures: CIS-fatigue +1.1 (95% CI -4.4 to +6.5, $p = 0.70$), SIP-8+59.1 (95% CI-201.7 to +319.8, $p = 0.65$), and IGFBP3/IGF1 ratio -0.5 (95% CI -2.8 to +1.7, $p = 0.63$). Conclusion: We found no differences in IGF1 status in CFS patients compared to healthy matched neighborhood controls. In addition, the results of this clinical trial do not demonstrate any benefit of Acclidyne over placebo in the treatment of CFS.

ter Wolbeek M., van Doornen L.J.P., Coffeng L.E., Kavelaars A., Heijnen C.J.

Cortisol and severe fatigue: A longitudinal study in adolescent girls

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847082840&partnerID=40>

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Fatigue is a common complaint among adolescents, especially in girls, and is associated with high rates of school absenteeism. Severe fatigue is often accompanied by psychological and physical symptoms. In the chronic fatigue syndrome (CFS) functioning of the hypothalamic-pituitary-adrenal (HPA)-axis has previously been found to be altered. The aim of the present study was to investigate whether cortisol production is deviant in fatigued adolescent girls from the general population and to study longitudinal changes in fatigue in association with possible changes in HPA-axis functioning. In the cross-sectional part of the study the cortisol response to awakening (CAR) and to a low-dose oral dexamethasone were examined in a group of fatigued adolescent girls ($n=87$) in comparison to a non-fatigued control group ($n=77$). Questionnaires regarding fatigue, depression, anxiety, sleep quality, somatic symptoms and CFS-related symptoms were filled out. Follow up measurements were performed after 6 and 12 months. While the fatigued and non-fatigued group differed remarkably on all symptom self-reports, no differences between groups in CAR and response to dexamethasone were observed. Girls in the fatigued group remained fatigued over time and reported high levels of other psychological and physical symptoms during the whole year of the study. The CAR varied between time points but correlated non-systematically with situational characteristics or symptom reports. We conclude that trait-like fatigue, as measured in a sample of adolescent girls from a high school population, is not reflected in a dysregulation as assessed on the level of salivary cortisol after awakening. © 2007 Elsevier Ltd. All rights reserved.

Rajeevan M.S., Smith A.K., Dimulescu I., Unger E.R., Vernon S.D., Heim C., Reeves W.C.
Glucocorticoid receptor polymorphisms and haplotypes associated with chronic fatigue syndrome

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Chronic fatigue syndrome (CFS) is a significant public health problem of unknown etiology, the pathophysiology has not been elucidated, and there are no characteristic physical signs or laboratory abnormalities. Some studies have indicated an association of CFS with deregulation of immune functions and hypothalamic-pituitary-adrenal (HPA) axis activity. In this study, we examined the association of sequence variations in the glucocorticoid receptor gene (NR3C1) with CFS because NR3C1 is a major effector of the HPA axis. There were 137 study participants (40 with CFS, 55 with insufficient symptoms or fatigue, termed as ISF, and 42 non-fatigued controls) who were clinically evaluated and identified from the general population of Wichita, KS. Nine single nucleotide polymorphisms (SNPs) in NR3C1 were tested for association of polymorphisms and haplotypes with CFS. We observed an association of multiple SNPs with chronic fatigue compared to non-fatigued (NF) subjects ($P < 0.05$) and found similar associations with quantitative assessments of functional impairment (by the SF-36), with fatigue (by the Multidimensional Fatigue Inventory) and with symptoms (assessed by the Centers for Disease Control Symptom Inventory). Subjects homozygous for the major allele of all associated SNPs were at increased risk for CFS with odds ratios ranging from 2.61 (CI 1.05-6.45) to 3.00 (CI 1.12-8.05). Five SNPs, covering a region of approximately 80 kb, demonstrated high linkage disequilibrium (LD) in CFS, but LD gradually declined in ISF to NF subjects. Furthermore, haplotype analysis of the region in LD identified two associated haplotypes with opposite alleles: one protective and the other conferring risk of CFS. These results demonstrate NR3C1 as a potential mediator of chronic fatigue, and implicate variations in the 5' region of NR3C1 as a possible mechanism through which the alterations in HPA axis regulation and behavioural characteristics of CFS may manifest. © 2006 Blackwell Publishing Ltd.

Jerjes W.K., Taylor N.F., Wood P.J., Cleare A.J.

Enhanced feedback sensitivity to prednisolone in chronic fatigue syndrome

2007 Psychoneuroendocrinology 32 (2); 192 – 198

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Objective: Enhancement of negative feedback control of the HPA axis in patients with chronic fatigue syndrome (CFS) has been reported using the low dose dexamethasone suppression test. We have developed the use of prednisolone (5 mg) as a more physiologically appropriate alternative to dexamethasone in the investigation of mild degrees of glucocorticoid resistance or supersensitivity. The objective of the study was to use this test to look for alterations in negative feedback control of the HPA axis in CFS patients. Methods: Fifteen patients with CFS were recruited after fulfilling strict criteria including the absence of comorbid psychiatric diagnosis. They collected urine between 0900 and 1800 h and saliva at 0900 h pre-prednisolone. At midnight, they took prednisolone (5 mg) orally and then collected urine and saliva at the same intervals the following day. Results: Salivary cortisol was lower in CFS subjects pre-prednisolone than controls. Urinary cortisol metabolites were

lower in CFS subjects pre-prednisolone, but did not reach significance. Both measures were significantly lower in CFS subjects post-dose. Mean percentage suppression of both salivary cortisol and urinary cortisol metabolites was significantly higher in CFS compared to controls. Conclusion: There is enhanced sensitivity of the HPA axis to negative feedback in CFS as demonstrated using the prednisolone suppression test. This provides further evidence of alterations in the control of the HPA axis in patients with established CFS. © 2007 Elsevier Ltd. All rights reserved.

Gupta S., Aslakson E., Gurbaxani B.M., Vernon S.D.

Inclusion of the glucocorticoid receptor in a hypothalamic pituitary adrenal axis model reveals bistability

2007 Theoretical Biology and Medical Modelling 4

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847184186&partnerID=40>

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Background. The body's primary stress management system is the hypothalamic pituitary adrenal (HPA) axis. The HPA axis responds to physical and mental challenge to maintain homeostasis in part by controlling the body's cortisol level. Dysregulation of the HPA axis is implicated in numerous stress-related diseases. **Results.** We developed a structured model of the HPA axis that includes the glucocorticoid receptor (GR). This model incorporates nonlinear kinetics of pituitary GR synthesis. The nonlinear effect arises from the fact that GR homodimerizes after cortisol activation and induces its own synthesis in the pituitary. This homodimerization makes possible two stable steady states (low and high) and one unstable state of cortisol production resulting in bistability of the HPA axis. In this model, low GR concentration represents the normal steady state, and high GR concentration represents a dysregulated steady state. A short stress in the normal steady state produces a small perturbation in the GR concentration that quickly returns to normal levels. Long, repeated stress produces persistent and high GR concentration that does not return to baseline forcing the HPA axis to an alternate steady state. One consequence of increased steady state GR is reduced steady state cortisol, which has been observed in some stress related disorders such as Chronic Fatigue Syndrome (CFS). **Conclusion.** Inclusion of pituitary GR expression resulted in a biologically plausible model of HPA axis bistability and hypocortisolism. High GR concentration enhanced cortisol negative feedback on the hypothalamus and forced the HPA axis into an alternative, low cortisol state. This model can be used to explore mechanisms underlying disorders of the HPA axis. © 2007 Gupta et al; licensee BioMed Central Ltd.

Grans H., Nilsson M., Dahlman-Wright K., Evengard B.

Reduced levels of oestrogen receptor β mRNA in Swedish patients with chronic fatigue syndrome

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Background: Chronic fatigue syndrome (CFS) is an illness with unknown aetiology and pathophysiology. The difference in incidence by sex observed for CFS indicates a role for oestrogen and oestrogen receptors in disease development. Furthermore, an immunomediated pathogenesis has been suggested for CFS, providing an additional connection to oestrogen, which displays immunomodular functions. **Aims:** To investigate a possible association of oestrogen receptor (ER) mRNAs and two ER β single-nucleotide polymorphisms (SNPs) with CFS. **Methods:** Messenger RNA levels of ER α , ER β wt and ER β cx were investigated in peripheral blood mononuclear cells from 30

patients with CFS and 36 healthy controls by quantitative real-time polymerase chain reaction. Two ER β SNPs were scored in the same material. Results: The CFS group showed significantly lower mRNA expression levels of ER β wt compared with the healthy control group. No differences were observed for ER β ± or ER β cx between patients and controls. There were no significant differences in frequency for the investigated ER β SNPs between cases and controls. Conclusions: The reduced ER β wt expression level observed in this study is consistent with an immune-mediated pathogenesis of CFS. Additionally, the observation that ER β wt expression is decreased in CFS could provide an entry point to identify interesting, potentially disease-causing, candidate molecules for further study. A possible connection between oestrogen, oestrogen receptors and CFS should be evaluated further.

Chen Y.-F., Yang W.-J., Fu S.-G., Zhang X.-D.

Effects of electro-acupuncture on hypothalamic-pituitary-adrenal index and corticotropin releasing hormone mRNA expression of rats with chronic fatigue syndrome

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Objective: To investigate the mechanism of electroacupuncture in treating chronic fatigue syndrome (CFS) in terms of the neuro-endocrine system by observing the regulative effect of EA on hypothalamic-pituitary-adrenal index (HPA index) and corticotropin releasing hormone mRNA (CRH mRNA) in CFS model rats. Methods: The rats were randomly divided into control group, model group, and electroacupuncture group. Model and electroacupuncture groups were forced to swim in cold water to make CFS model, while rats in electroacupuncture group were treated with electroacupuncture treatment at the same time. Electroacupuncture group was given at Baihui (GV 20) and Zusanli (ST 36). Evaluation of the model was processed according to the behavior changes of the rats. Hypothalamic, pituitary, and adrenal were weighted to calculate HPA index. CRH mRNA in hypothalamus was measured by fluorescence quantitative polymerase chain reaction (FQPCR). Results: The model rats had behavior changes, and both physical and mental fatigue was observed. HPA index raised and expression of CRH mRNA in hypothalamus increased in CFS rats. After electroacupuncture treatment, the physical and mental fatigue was improved, and the hypothalamic index and CRH mRNA decreased significantly, while the pituitary and adrenal index only had little decrease. Conclusion: Cold water swim press could mimic the pathogenesis and make similar manifestations in rats with the common clinical symptoms. CFS has close relationship with increase of HPA index and CRH mRNA expression. Electroacupuncture can regulate the function of HPA axis to deal with CFS. © Shanghai Research Institute of Acupuncture and Meridian 2007.

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Possible mechanisms of the formation of chronic fatigue syndrome in the clinical picture of multiple sclerosis

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A frequent manifestation of multiple sclerosis (MS) is chronic fatigue syndrome, which can be defined as a subjective decrease in the level of physical and/or mental energy. Chronic fatigue syndrome can be divided into asthenia (fatigue at rest), pathological fatigability (fatigue on physical loading), and fatigue on the background of deterioration of other symptoms (exacerbation of MS). There are both central and peripheral mechanisms for the formation of fatigue. The combination of fatigue and affective disturbances, especially depression and sleep disorders (insomnia, restless legs syndrome) is common in MS and may provide evidence that they share common mechanisms -

decreases in the activity of the serotonergic and noradrenergic systems. An important component in the formation of chronic fatigue syndrome consists of endocrine and autoimmune factors, the latter having a greater effect on asthenia than on pathological fatigue. Further studies of the pathogenetic mechanisms of the formation of asthenia and pathological fatigue and clarification of their differential diagnostic signs should allow not only a better understanding of the nature of this syndrome, but also better selection of individual treatment. © Springer Science+Business Media, Inc. 2007.

Wilbur J., Shaver J., Kogan J., Buntin M., Wang E.
Menopausal transition symptoms in midlife women living with fibromyalgia and chronic fatigue

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We aimed to determine how menopausal transition symptoms cluster across 216 midlife women with fibromyalgia, chronic fatigue syndromes (FMS/CFS), or both and subsequently to compare symptom factor severity scores by menopausal status among these women and compare symptom reporting with prior community-based samples of women without obvious illness. We designed a cross-sectional telephone survey of 216 women aged 35 to 55, diagnosed with FMS/CFS, symptomatic in the prior 6 months, and without hysterectomy. Thirty-six of 61 symptoms loaded on five factors: aroused/anxious mood, depressed mood/withdrawal, musculoskeletal, gastrointestinal (GI), and vasomotor. Peri- and postmenopausal women had higher symptom severity scores for musculoskeletal, GI, and vasomotor factors but not mood factors. Symptoms for the women we studied who had FMS/CFS clustered similar to those in previous community-based samples of midlife women without major illness; however, the number of women experiencing symptoms was much higher among our sample. Copyright © Taylor & Francis Group, LLC.

Van Heukelom R.O., Prins J.B., Smits M.G., Bleijenberg G.
Influence of melatonin on fatigue severity in patients with chronic fatigue syndrome and late melatonin secretion

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The effect of melatonin, a chronobiotic drug, was explored in 29 patients with chronic fatigue syndrome (CFS) and Dim Light Melatonin onset (DLMO) later than 21.30 hours, reflective of delayed circadian rhythmicity. The patients took 5 mg of melatonin orally, 5 h before DLMO during 3 months. Their responses to the checklist individual strength (CIS), a reliable questionnaire measuring the severity of personally experienced fatigue, were assessed twice with a 6-week interval immediately before the treatment and once after 3 months treatment. In the pre-treatment period the fatigue sub-score improved significantly. After treatment, the total CIS score and the sub-scores for fatigue, concentration, motivation and activity improved significantly. The sub-score fatigue normalized in two of the 29 patients in the pre-treatment period and in eight of 27 patients during treatment. This change was significant. In the patients with DLMO later than 22.00 hours (n = 21) the total CIS score and the sub-scores for fatigue, concentration and activity improved significantly more than in the patients (n = 8) with DLMO earlier than 22.00 hours. Melatonin may be an effective treatment for patients with CFS and late DLMO, especially in those with DLMO later than 22.00 hours. © 2006 EFNS.

Mommersteeg P.M.C., Heijnen C.J., Verbraak M.J.P.M., Van Doornen L.J.P.

Clinical burnout is not reflected in the cortisol awakening response, the day-curve or the response to a low-dose dexamethasone suppression test

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Burnout is presumed to be the result of chronic stress, and chronic stress is known to affect the HPA-axis. To date, studies on HPA-axis functioning in burnout have showed inconsistent results. In the present study, a large sample (n=74) of clinically diagnosed burnout individuals, mostly on sick-leave, were included and compared with 35 healthy controls. Salivary cortisol was sampled on 2 days to determine the cortisol awakening response (CAR) and the day-curve. In addition, the dexamethasone suppression test (DST) was applied to assess the feedback efficacy of the HPA-axis. There were no differences observed in the CAR, day-curve or CAR after DST in the burnout group as compared to a healthy control group. Burnout shows overlap in symptoms with chronic fatigue syndrome (CFS) and depression. Therefore, differential changes in HPA-axis functioning that resemble the hypo-functioning of the HPA-axis in CFS, or rather the hyper-functioning of the HPA-axis in depression, might have obscured the findings. However, no effect of fatigue or depressive mood on HPA-axis functioning was found in the burnout group. We concluded that HPA-axis functioning in clinically diagnosed burnout participants as tested in the present study, seems to be normal. © 2005 Elsevier Ltd. All rights reserved.

Jerjes W.K., Taylor N.F., Peters T.J., Wessely S., Cleare A.J.

Urinary cortisol and cortisol metabolite excretion in chronic fatigue syndrome

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OBJECTIVES: Reduced basal hypothalamic-pituitary-adrenal (HPA) axis output in chronic fatigue syndrome (CFS) has been inferred from low cortisol levels in blood, saliva, and urine in some studies. Because > 95% of cortisol is metabolized before excretion, we assessed cortisol output by assay of both cortisol metabolites and free cortisol in 24-hour urine collections and also investigated sex differences in these between CFS and control groups. **METHOD:** We calculated total urinary cortisol metabolites (TCM) and cortisol metabolite ratios from individual steroid data in 40 patients (20 males and 20 females) with CFS who were free of medication or comorbid psychiatric disorder likely to influence the HPA axis. Results were compared with those of 40 healthy volunteers (20 males and 20 females) well matched for age and body mass index. Data for free cortisol was obtained on 28 of the patients and 27 of the controls. **RESULTS:** The mean of TCM and cortisol metabolite ratios was not significantly different between patients and controls for either sex ($p > .05$ for all parameters). Previously established sex differences were confirmed in our controls and were found to be similar in CFS for TCM and the ratios 11OH/11OXO, $5\alpha/5\beta$ THF, and 20OH/20OXO (see text) ($p < .005$, $p < .05$, $p < .05$, and $p < .005$, respectively). Urinary free cortisol values were numerically (but not statistically) lower in patients with CFS than controls, and correlated inversely with fatigue levels in patients. **CONCLUSION:** The finding of normal urinary cortisol metabolite excretion in patients with CFS is at variance with earlier reports that CFS is a hypocortisolemic state. If serum and saliva cortisol levels are lower in CFS, this would suggest that metabolic clearance of

cortisol is faster in patients with CFS than controls. This study also demonstrates that sex differences must be taken into account when interpreting results in patients with CFS. Copyright © 2006 by the American Psychosomatic Society.

Jerjes W.K., Peters T.J., Taylor N.F., Wood P.J., Wessely S., Cleare A.J.
Diurnal excretion of urinary cortisol, cortisone, and cortisol metabolites in chronic fatigue syndrome

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Objective: The aim of this study was to obtain comprehensive information on basal hypothalamic-pituitary-adrenal (HPA) axis activity in chronic fatigue syndrome (CFS) patients who were not affected by medication or comorbid psychiatric disorder likely to influence the HPA axis. Method: Steroid analysis of urine collections from 0600 to 2100 h at 3-h intervals in CFS patients and in controls. Results: Urinary free cortisol and cortisone concentrations showed a significant normal diurnal rhythm, but levels were lower across the cycle in CFS. In contrast, while urinary cortisol metabolites also showed a normal diurnal rhythm, levels were not significantly different between the CFS and controls at any time. Derived metabolite ratios were similar in both groups. Conclusion: This study provides further evidence for reduced basal HPA axis function in patients with CFS, based on lower free cortisol and cortisone levels, but this is not corroborated by cortisol metabolite data. The difference between these measures cannot be explained by an altered timing of the diurnal rhythm. © 2006 Elsevier Inc. All rights reserved.

Chalmers R.A., Jones M.G., Goodwin C.S., Amjad S.
CFSUM1 and CFSUM2 in urine from patients with chronic fatigue syndrome are methodological artefacts

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-31044444362&partnerID=40>

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McGregor et al. reported increased levels of an unidentified urinary compound (CFSUM1) in patients with chronic fatigue syndrome (CFS), with reduced excretion of another unidentified compound (CFSUM2), and suggested the possibility of chemical or metabolic 'markers' for CFS. The identity of CFSUM1 as reported was erroneous and the identities of these compounds have remained unknown until now. Urine samples were obtained from 30 patients with ME/CFS, 30 age- and sex-matched healthy controls, 20 control patients with depression and 22 control patients with rheumatoid arthritis. Samples were prepared using the published methods of McGregor et al. to produce heptafluorobutyryl-isobutyl derivatives of urinary metabolites. Alternative preparations utilised isopropyl, n-butyl and trifluoroacetyl derivatives. These were separated and identified using gas chromatography-mass spectrometry. CFSUM2 was identified as being partially derivatised [isobutyl ester-mono-heptafluorobutyryl (HFB)] serine. CFSUM1 was identified as partially derivatised pyroglutamic acid, being the isobutyl ester without formation of a HFB derivative. Both CFSUM1 and CFSUM2 are artefacts of the sample preparation procedure and previously reported quantitative

abnormalities of CFSUM1 and CFSUM2 in urine from patients with ME/CFS are also artefactual. Pyroglutamic acid may be of primarily dietary origin. The methods used cannot provide reliable qualitative or quantitative data on urinary metabolites. No clinical or biochemical significance can be drawn between these compounds in ME/CFS or any other clinical conditions. © 2005 Elsevier B.V. All rights reserved.

Shi S.-D., Zhou M.-W., Li J.-J., Shi J.-H.

Behavioral and neuroendocrinological changes in mice with chronic stress-related fatigue and interventions of yixinle oral liquid

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Background: Chronic fatigue syndrome (CFS) is a chronic disease, with which the patients have difficulty in taking traditional Chinese medicine decoction. So it is necessary to accumulate the special prescriptions for CFS. Based on the principle of nourishing-yin-and-replenishing-kidney and filling-up-essence-and-producing-an-effect-toward-clear-vision, American ginseng, aweto, Tortoise Shell and cornus officinalis were selected and were made into a compound preparation by using modern pharmaceutical technique. Objective: To establish the animal model of chronic stress-related fatigue for observations on the effects of yi xin le oral Liquid (YXL) on behavioral and neuroendocrinological changes in rats. Design: It was a randomized controlled study. Setting: Medical Study Department, Guangzhou General Hospital of Guangzhou Military Area Command of Chinese PLA; Department of Obstetrics and Gynecology, Panyu-shigi People's Hospital of Guangzhou city of Guangdong Province. Materials: The experiment was conducted at the Laboratory Center of Guangzhou General Hospital of Guangzhou Military Area Command of Chinese PLA from August to December 2003. Sixty Kunming mice were selected and divided into 5 groups, as normal group, model group, Ejiao (EJ) compound group, small dose YXL group and large dose YXL group, with 12 mice in each group. YXL was produced by the Medical Research Department of Guangzhou LiuHuaQiao Hospital (1mL YXL was made from 1g raw materials, with a lot number of 030618). EJ compound was produced by Shandong Dong-E E-Jiao CO.,LTD, with lot number of 030425. Water maze was supplied by Institute of Materia Medica, Chinese Academy of Medical Sciences. Methods: All the animals were fed in clean level room at $(20\pm 2)^{\circ}\text{C}$, five mice in one cage, with free food and water supply. After 1-2 days, they were used for establishing animal model. Except for mice in normal group, mice in other groups swam in cold water at $(10\pm 1)^{\circ}\text{C}$, in duration of 6.0-9.5 minutes for each time. Additionally, in EJ group, mice received EJ at a dose of 50 g/(kg \cdot d). In small dose YXL group, mice received YXL at a dose of 25 g/(kg \cdot d). In large dose of YXL group, mice received YXL at a dose of 50 g/(kg \cdot d). In normal group and model group, mice received saline at a dose of 0.5 mL for each time, twice a day and in a duration of 9 days. After establishing the animal model, spontaneous exploratory activity of mice and the forced-swim time was assessed (time spent in the middle of open field or to traversing the field, times to traversing the test field, time spent in orientating while upright or decoration and exploring times before orientating while upright or decoration were measured by open field test). After tests, blood samples were taken from carotid artery and the animals were decollated under anesthesia. Immediately, their adrenal glands were taken out under axenic condition. And the serum level of monoamine neurotransmitter was measured by high performance liquid chromatography HPLC and electrochemical devices. The concentration of vitamin C in adrenal gland was detected using 2,4 dinitrophenylhydrazine colorimetric method. Main outcome measures: After treatment, the spontaneous exploratory activity, and the forced-swim time, the vitamin C content in adrenal gland and the changes in monoamine neurotransmitter and its metabolites were measured. Results: All the 60 mice in the experiment entered the statistical analysis. 1 Comparison of changes in the time spent in the middle of the open field among all the groups: Compared with control group, significantly longer time was spent in model group [(6.64 \pm 3.73), (13.80 \pm 6.70) s, P <0.01]. Compared with model group,

significantly shorter time was spent in EJ group, small dose YXL group and large dose YXL group [(13.80 \bar{A} \pm 6.70), (5.12 \bar{A} \pm 2.62), (4.51 \bar{A} \pm 1.43), (3.34 \bar{A} \pm 2.01)s, P < 0.05,P < 0.05,P < 0.01]. Compared with EJ group, significantly shorter time was spent in small dose YXL group and large dose YXL group (P < 0.05,P < 0.01). 2 Comparison of the forced-swim time after cold water stress among all the groups: Compared with control group, significantly shorter time was spent in model group [(176.44 \bar{A} \pm 38.02), (145.01 \bar{A} \pm 59.51)minutes, P < 0.01]. Compared with model group, significantly longer time was spent in EJ group, small dose YXL group and large dose YXL group [(145.01 \bar{A} \pm 59.51), (172.73 \bar{A} \pm 71.59), (181.91 \bar{A} \pm 38.60), (186.59 \bar{A} \pm 50.81)minutes,P < 0.05,P < 0.05,P < 0.01]. Compared with EJ group, significantly longer time was spent in small dose YXL group and large dose YXL group (P < 0.05,P < 0.01). 3 Comparison of the vitamin C content in adrenal gland after cold water stress in all the groups: Compared with control group, significantly lower vitamin C content in adrenal gland was detected in model group [(3 951+280),(3 546 \bar{A} \pm 408) \bar{I} $\frac{1}{4}$ g/g,P < 0.01]. Compared with model group, significantly higher vitamin C content in adrenal gland was detected in EJ group, small dose YXL group and large dose YXL group [(3546 \bar{A} \pm 408), (3 978 \bar{A} \pm 288),(4 068 \bar{A} \pm 672),(4 248 \bar{A} \pm 704) \bar{I} $\frac{1}{4}$ g/g,P < 0.05,P < 0.05,P < 0.01]. Compared with EJ group, significantly higher vitamin C content in adrenal gland was detected in large dose YXL group (P < 0.05). 4 Comparison of the levels of monoamine neurotransmitter and its metabolites after cold water stress in all the groups: Compared with control group, adrenalin and dopamine were significantly higher in model group [(175 \bar{A} \pm 56) nmol/L, (258 \bar{A} \pm 97) nmol/L; (1 804 \bar{A} \pm 889) nmol/L, (4 049 \bar{A} \pm 1 443) nmol/L, P < 0.01], while 5-Hydroxyindole Acetic Acid (5-HIAA) was decreased [(129.05 \bar{A} \pm 34.19), (117.78 \bar{A} \pm 42.86) nmol/L, P < 0.05]. Compared with model group, adrenalin and dopamine were significantly lower in EJ group, small dose YXL group and large dose YXL group [(258 \bar{A} \pm 97), (256 \bar{A} \pm 135), (230 \bar{A} \pm 113),(198 \bar{A} \pm 88) nmol/L,P < 0.05,P < 0.01; (4 049 \bar{A} \pm 1443), (3 702 \bar{A} \pm 1 266), (2 630 \bar{A} \pm 939), (1 903 \bar{A} \pm 658) nmol/ L,P < 0.05,P < 0.01,P < 0.01], while 5-HLAA was significantly higher [(117.78 \bar{A} \pm 42.86), (138.57 \bar{A} \pm 50.43), (155.07 \bar{A} \pm 35.31), (236.21 \bar{A} \pm 49.82) nmol/L, P < 0.05,P < 0.05,P < 0.01]. Compared with EJ group, adrenalin and dopamine were significantly lower in small dose YXL group and large dose YXL group (P < 0.05,P < 0.01), and compared with EJ group, the 5-HIAA was significantly higher in large dose YXL group (P < 0.01). Conclusion: YXL can promote the spontaneous exploratory activity, the forced-swim time and the adrenalin level in mice CFS model. It can also regulate the imbalance of serum monoamine neurotransmitter level and hereby to have the benefits of anti-fatigue, anti-stress and regulations on neuroendocrinological system.

Segal T.Y., Hindmarsh P.C., Viner R.M.

Disturbed adrenal function in adolescents with chronic fatigue syndrome

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University College London Hospitals, University College London, London, United Kingdom; London Ctr. for Paediat. Endocrinol., University College London, London, United Kingdom; Middlesex Hospital, Mortimer Street, London W1T 3AA, United Kingdom

Objective: To investigate adrenal function in children and adolescents with chronic fatigue syndrome (CFS) compared with age-matched controls. Methods: Case-control study of low dose (500 ng/m²) synacthen tests (LDST) in 23 adolescents with CFS and 17 age-matched controls. Serum cortisol concentrations were measured at 5-min intervals from 10 to 45 minutes. Peak serum cortisol concentration, time to peak, rise in cortisol and area under the curve (AUC) were derived. Results: Patients with CFS had significantly lower mean cortisol levels during the LDST (p <0.001), lower peak cortisol (p <0.025), reduced cortisol AUC (p <0.005) and longer time to peak cortisol (p <0.05). Abnormalities were seen in both sexes but were more pronounced in females. Unstimulated adrenal androgen and 17-hydroxy-progesterone concentrations were normal. Conclusions: Adolescents with CFS have subtle alterations in adrenal function suggesting a reduction in central stimulation of the adrenal glands. The more pronounced effects in females may reflect differential central effects of stress on hypothalamic-pituitary-adrenal axis regulation between the sexes. © Freund Publishing House Ltd., London.

Rubin G.J., Hotopf M., Papadopoulos A., Cleare A.
Salivary cortisol as a predictor of postoperative fatigue

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Objective: Some patients with chronic fatigue syndrome (CFS) exhibit low basal cortisol levels, but it is not known whether low cortisol is a cause of CFS, predates the onset of CFS symptoms, or is an epiphenomenon caused by the behavioral changes typical of CFS. Because elective surgery is one of the few predictable risk factors for chronic fatigue, in this study, we followed a cohort of surgery patients from before to 6 months after their operation to test these theories. Method: One hundred sixty-one patients completed fatigue questionnaires and provided salivary cortisol samples before undergoing an elective inpatient surgical procedure, and then 2 days, 3 weeks, and 6 months afterward. Results: Controlling for relevant demographic and surgical variables and for preoperative fatigue, low preoperative cortisol did not predict postoperative fatigue severity on any occasion ($p > .05$). Similarly, there was no correlation between low postoperative cortisol and postoperative fatigue severity at 3 weeks or 6 months ($p > .05$). Although 16 patients met our case definition for "chronic fatigue" at the 6-month follow up, low preoperative and low postoperative cortisol did not significantly predict fatigue caseness ($p > .05$). Conclusions: Any association between chronic fatigue and low cortisol would seem to develop after the onset of fatigue symptoms. Low cortisol is therefore unlikely to be the primary cause of chronic fatigue states. Copyright © 2005 by the American Psychosomatic Society.

Jones M.G., Goodwin C.S., Amjad S., Chalmers R.A.
Plasma and urinary carnitine and acylcarnitines in chronic fatigue syndrome

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Contradictory reports have suggested that serum free carnitine and acylcarnitine concentrations are decreased in patients with chronic fatigue syndrome (CFS) and that this is a cause of the muscle fatigue observed in these patients. Others have shown normal serum free carnitine and acylcarnitines in similar patients. We report here studies on free, total and esterified (acyl) carnitines in urine and blood plasma from UK patients with CFS and three control groups. Plasma and timed urine samples were obtained from 31 patients with CFS, 31 healthy controls, 15 patients with depression and 22 patients with rheumatoid arthritis. Samples were analysed using an established radioenzymatic procedure for total, free and esterified (acyl) carnitine. There were no significant differences in plasma or urinary total, free or esterified (acyl) carnitine between UK patients with CFS and the control groups or in renal excretion rates of these compounds. The data presented here show that, in the CFS patients studied, there are no significant abnormalities of free or esterified (acyl) carnitine. It is thus unlikely that abnormalities in carnitine homeostasis have any significant role in the aetiology of their chronic fatigue. © 2005 Elsevier B.V. All rights reserved.

Jerjes W.K., Cleare A.J., Wessely S., Wood P.J., Taylor N.F.

Diurnal patterns of salivary cortisol and cortisone output in chronic fatigue syndrome

2005 Journal of Affective Disorders 87 (02-Mar); 299 – 304

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Department of Clinical Biochemistry, King's College Hospital, Denmark Hill, London SE5 9RX, United Kingdom; Department of Psychological Medicine, Institute of Psychiatry, King's College London, London SE5 8AZ, United Kingdom; National Affective Disorders Unit, Bethlem Royal and Maudsley Hospitals, London SE5 8AF, United Kingdom; Chronic Fatigue Syndrome Unit, King's College Hospital, London SE5, United Kingdom; Regional Endocrine Unit, Southampton General Hospital, Southampton SO16 6YD, United Kingdom Background: The aim of the present study was to obtain a naturalistic measure of diurnal hypothalamic-pituitary-adrenal (HPA) axis output in CFS patients unaffected by medication or comorbid psychiatric disorder likely to influence the axis. Method: Cortisol and cortisone levels were measured in saliva samples collected from 0600 h to 2100 h at 3-h intervals in CFS patients and healthy controls. Results: Mean cortisol and cortisone concentrations were significantly lower in patients than controls across the whole day, as were levels at each individual time point except 2100 h. Cosinor analysis showed a significant diurnal rhythm of cortisol and cortisone that was not phase-shifted in CFS compared to controls. However, there was a lower rhythm-adjusted mean and a lower amplitude in CFS patients. The cortisol/cortisone ratio showed no diurnal rhythm and did not differ between CFS subjects and controls. Limitations: The sample size was relatively small, and drawn from specialist referral patients who had been ill for some time; generalisation of these results to other populations is therefore unwarranted. Conclusion: The main findings of this study are to provide further evidence for reduced basal HPA axis function in at least some patients with CFS and to show for the first time that salivary cortisone is also reduced in CFS and has a diurnal rhythm similar to that of cortisol. We have also demonstrated that the cortisol/cortisone ratio remains unchanged in CFS, suggesting that increased conversion of cortisol to cortisone cannot account for the observed lowering of salivary cortisol. © 2005 Elsevier B.V. All rights reserved.

Izgi H.B., Gokce C., Calis M., Turan T., Kirnap M., Sofuoglu S., Durak A.C., Tutus A., Kelestimur F. Investigation of the hypothalamopituitary-adrenal axis by low-dose (1 $\frac{1}{4}$ g) adrenocorticotrophic hormone test and metyrapone test in patients with chronic fatigue syndrome

2005 Endocrinologist 15 (2); 89 - 92

<http://www.scopus.com/inward/record.url?eid=2-s2.0-15244350171&partnerID=40>

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Chronic fatigue syndrome (CFS) is a disease characterized by debilitating fatigue of at least 6 months' duration. The pathophysiology and the localization of the underlying HPA axis disturbance are a matter of debate. Our aim was to evaluate the hypothalamopituitary-adrenal (HPA) axis by the 1 $\frac{1}{4}$ g adrenocorticotrophic hormone (ACTH) test and metyrapone test in patients with CFS and to compare the size of the adrenal glands of the patients with that of the control subjects. Twenty patients (14 females, 6 males) with CFS were included in the study. Fifteen healthy subjects (12 females, 3 males) served as matched controls. ACTH stimulation test was carried out by using 1 $\frac{1}{4}$ g ACTH, intravenously, as a bolus injection after an overnight fast, and blood samples for cortisol were drawn at 0, 30, and 60 minutes. Metyrapone at a dosage of 30 mg/kg was taken orally at 11:00 PM with a snack. The following morning, blood was sampled for serum 11-deoxycortisol between 8:00 and 9:00 AM. Peak cortisol responses to 1 $\frac{1}{4}$ g ACTH test were significantly lower in the CFS group (620.7 \pm 146.2 nmol/L) than in the control group (838.7 \pm 129.6 nmol/L) ($P < 0.05$). The lowest peak cortisol response after the 1 $\frac{1}{4}$ g ACTH test was 575.8 nmol/L in normal subjects. Nine patients with CFS had peak cortisol responses to 1 $\frac{1}{4}$ g ACTH test lower than 575.8 nmol/L. 11-

deoxycortisol response to metyrapone was significantly lower in the patients with CFS (114.2 ± 31.1 nmol/L) than in the healthy subjects (186.5 ± 15.7 nmol/L) ($P < 0.05$). The lowest 11-deoxycortisol level after metyrapone in the controls was 168.3 nmol/L. Nineteen of 20 patients with CFS had lower 11-deoxycortisol level after metyrapone than detected in normal subjects. Eight patients had both subnormal 11-deoxycortisol response to metyrapone and subnormal cortisol response to $1 \frac{1}{4}$ g ACTH test. On the other hand, 10 patients had subnormal 11-deoxycortisol response to metyrapone but normal cortisol response to $1 \frac{1}{4}$ g ACTH test. Thickness of the right and left adrenal glands were similar between the patients with CFS and healthy subjects ($P > 0.05$). We conclude that the perturbation of the HPA axis in CFS is characterized by underactivation of the HPA axis. Copyright © 2005 by Lippincott Williams & Wilkins.

Inder W.J., Prickett T.C.R., Mulder R.T.
Normal opioid tone and hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome despite marked functional impairment

2005 Clinical Endocrinology 62 (3); 343 - 348

<http://www.scopus.com/inward/record.url?eid=2-s2.0-15044338557&partnerID=40>

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Objective: To determine whether the functional impairment seen in chronic fatigue syndrome (CFS) is associated with reduced levels of central opioids and/or deficiency of the hypothalamic-pituitary-adrenal (HPA) axis. Design: Single-blinded case-control study measuring functional and psychological status, basal hormonal parameters and ACTH/cortisol response to naloxone and ovine corticotrophin-releasing hormone (oCRH) vs. placebo in people with CFS and healthy controls. Patients: Twelve people with CFS and 11 age-matched controls. Measurements: Hormonal parameters: basal levels of 09:00 h plasma cortisol, dehydroepiandrosterone sulfate (DHEAS) and IGF-1. 24-h urinary free cortisol. Plasma ACTH and cortisol response to naloxone $125 \frac{1}{4}$ g/kg, oCRH $1 \frac{1}{4}$ g/kg and placebo (normal saline). Psychological parameters: SF-36, Hamilton Depression Score, Hospital Anxiety and Depression Scale and Fatigue Scale. Results: There were highly significant differences between the CFS subjects and the controls with respect to the measures of fatigue and physical functioning. However, there were no differences in basal levels of 09:00 h cortisol (367 ± 37 vs. 331 ± 39 nmol/l, $P = 0.51$), DHEAS (4.2 ± 0.6 vs. $4.0 \pm 0.5 \frac{1}{4}$ mol/l, $P = 0.81$), 24-h urinary free cortisol (182 ± 27 vs. 178 ± 21 nmol/24 h, $P = 0.91$) or IGF-1 (145 ± 19 vs. $130 \pm 11 \frac{1}{4}$ g/l, $P = 0.52$) between the CFS group and controls, respectively. There was also no difference between the groups with respect to the ACTH and cortisol response to either oCRH or naloxone. Conclusions: Our data do not support an aetiological role for deficiency in central opioids or the HPA axis in the symptoms of CFS. © 2005 Blackwell Publishing Ltd.

Di Giorgio A., Hudson M., Jerjes W., Cleare A.J.
24-Hour pituitary and adrenal hormone profiles in chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-19444363250&partnerID=40>

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Objectives: Disturbances of neuroendocrine function, particularly the hypothalamo-pituitary-adrenal (HPA) axis, have been implicated in the pathophysiology of chronic fatigue syndrome (CFS).

However, few studies have attempted to measure blood levels of pituitary or adrenal hormones across a whole 24-hour period in CFS, and those that did so have used infrequent sampling periods. Our aim was to assess 24-hour pituitary and adrenal function using frequent blood sampling. Methods: We recruited 15 medication-free patients with CFS without comorbid psychiatric disorder and 10 healthy control subjects. Blood samples were collected over 24 hours and assayed for cortisol, corticotropin (ACTH), growth hormone (GH), and prolactin (PRL) levels on an hourly basis during daytime hours (10 AM to 10 PM) and every 15 minutes thereafter (10 PM to 10 AM). Results: Repeated-measures analyses of variance were undertaken using hormone levels averaged over 2-hour blocks to smooth curves by reducing the influence of sample timing relative to secretory burst. For ACTH, there was both a main effect of group, suggesting reduced mean ACTH secretion in patients with CFS over the whole monitoring period, and a group-by-time interaction, suggesting a differential pattern of ACTH release. Post hoc analysis showed reduced ACTH levels in CFS during the 8 AM to 10 AM period. In contrast, there were no significant abnormalities in the levels of cortisol, GH, and PRL in patients with CFS over the full cycle compared with control subjects. Cosinor analysis found no differences in the cortisol circadian rhythm parameters, but the ACTH rhythm did differ, patients with CFS showing an earlier acrophase. Conclusions: Patients with CFS demonstrated subtle alterations in HPA axis activity characterized by reduced ACTH over a full circadian cycle and reduced levels during the usual morning physiological peak ACTH secretion. This provides further evidence of subtle dysregulation of the HPA axis in CFS. Whether this dysregulation is a primary feature of the illness or instead represents a biologic effect secondary to having the illness itself remains unclear. Copyright © 2005 by the American Psychosomatic Society.

Badawy A.A.-B., Morgan C.J., Llewelyn M.B., Albuquerque S.R.J., Farmer A.
Heterogeneity of serum tryptophan concentration and availability to the brain in patients with the chronic fatigue syndrome

2005 Journal of Psychopharmacology 19 (4); 385 – 391

<http://www.scopus.com/inward/record.url?eid=2-s2.0-22344447987&partnerID=40>

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We assessed the serotonin status of patients with the chronic fatigue syndrome (CFS). Tryptophan (Trp) availability to the brain, expressed as the ratio of concentration of serum Trp to the sum of those of its five competitors (CAA), and other parameters of Trp disposition were compared in 23 patients with the CFS and 42 healthy controls. The serum [free Trp]/[CAA] ratio was 43% higher in CFS patients, due to a 48% higher [free Trp]. [Total Trp] was also significantly higher (by 19%) in CFS patients, and, although the [total Trp]/[CAA] ratio did not differ significantly between the control and patient groups, the difference became significant when the results were co-varied with age and gender. [CAA] was not significantly different between groups, but was significantly lower in females, compared to males, of the CFS patient group. We have established normal ranges for Trp disposition parameters and propose criteria for defining the serotonin-biosynthetic status in humans. We have provisionally identified two subgroups of CFS patients, one with normal serotonin and the other with a high serotonin status. The relevance of our findings to, and their implications for, the pharmacological and other therapies of the chronic fatigue syndrome are discussed. © 2005 British Association for Psychopharmacology.

Yamamoto S., Ouchi Y., Onoe H., Yoshikawa E., Tsukada H., Takahashi H., Iwase M., Yamaguti K., Kuratsune H., Watanabe Y.

Reduction of serotonin transporters of patients with chronic fatigue syndrome

2004 NeuroReport 15 (17); 2571 - 2574

<http://www.scopus.com/inward/record.url?eid=2-s2.0-19944428909&partnerID=40>

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To assess the involvement of serotonin in the symptoms of chronic fatigue syndrome, we investigated the serotonergic neurotransmitter system of chronic fatigue syndrome patients by the positron emission tomography (PET). Here we show that the density of serotonin transporters (5-HTTs) in the brain, as determined by using a radiotracer, [11C](+)McN5652, was significantly reduced in the rostral subdivision of the anterior cingulate as compared with that in normal volunteers. This subdivision is different from that in the dorsal anterior cingulate in which binding potential values of individual patient showed a weak negative correlation with self-reported pain score of the patients. Therefore, an alteration of serotonergic system in the rostral anterior cingulate plays a key role in pathophysiology of chronic fatigue syndrome. © 2004 Lippincott Williams & Wilkins.

Tryon W.W., Jason L., Frankenberry E., Torres-Harding S.

Chronic fatigue syndrome impairs circadian rhythm of activity level

2004 Physiology and Behavior 82 (5); 849 – 853

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4644363331&partnerID=40>

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Some of the symptoms of chronic fatigue syndrome (CFS) are the same as for disrupted circadian rhythm. Activity level is frequently used to study circadian rhythm. Continuous waist activity measurements taken every minute 24 h/day for from 5 to 7 days in 10 controls and from 2 to 7 days in 8 patients with CFS yielded two primary findings: (a) lower daytime activity and (b) less regular activity-rest cycles in persons with CFS than in controls. © 2004 Elsevier Inc. All rights reserved.

Torres-Harding S.R., Jason L.A., Turkoglu O.D.

Family medical history of persons with chronic fatigue syndrome

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Background: Little research has examined the family history of persons with CFS, although a few studies have found people with CFS may be more likely to have family members with fatigue or CFS-like conditions, cancers, autoimmune illness, and early parental death. Research into the family history of fatigue, chronic fatigue syndrome, and other medical or psychiatric illness may help inform the etiology of this illness. Objectives: The present investigation examined the occurrence of medical and psychiatric illness in the family history of persons with CFS, and then compared these results

with the family history of medical illness reported by a control group of persons without fatigue. Methods: Family medical history data was obtained from questionnaire responses, a medical assessment, and medical records, and were then classified into specific illness categories, using the International Classification of Diseases, Tenth Revision (ICD-10). Family history data was compared among three groups using logistic regression analyses. Results: Results indicated that persons with chronic fatigue syndrome were significantly more likely to report a family history of endocrine/metabolic disorders when compared to the control group. Conclusions: Findings suggest an underlying familial predisposition toward the development of both CFS and endocrine/metabolic disorders. This finding is consistent with the hypothesis that CFS represents a deregulation of the endocrine system. © 2004 by The Haworth Press, Inc. All rights reserved.

Torpy D.J., Bachmann A.W., Gartside M., Grice J.E., Harris J.M., Clifton P., Easteal S., Jackson R.V., Whitworth J.A.

Association between chronic fatigue syndrome and the corticosteroid-binding globulin Gene ALA SER224 polymorphism

2004 Endocrine Research 30 (3); 417 - 429

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Chronic fatigue syndrome (CFS) is characterized by idiopathic fatigue of greater than 6 months' duration with postexertional exacerbation and many other symptoms. A trend toward relative hypocortisolism is described in CFS. Twin and family studies indicate a substantial genetic etiologic component to CFS. Recently, severe corticosteroid-binding globulin (CBG) gene mutations have been associated with CFS in isolated kindreds. Human leukocyte elastase, an enzyme important in CBG catabolism at inflammatory sites, is reported to be elevated in CFS. We hypothesized that CBG gene polymorphisms may act as a genetic risk factor for CFS. A total of 248 patients with CFS defined by Centers for Disease Control criteria, and 248 controls were recruited. Sequencing and restriction enzyme testing of the CBG gene coding region allowed detection of severe CBG gene mutations and a common exon 3 polymorphism (c.825G→T, Ala-Ser 224). Plasma CBG levels were measured in 125 CFS patients and 198 controls by radioimmunoassay. Total and free (calculated and measured) cortisol levels were ascertained in single samples between 8-10 a.m. The age of onset (mid 30s) and gender ratio (2.2:1, female:male) of the patients were similar to those reported in U.S. epidemiologic studies. A trend toward a preponderance of serine224 homozygosity among the CFS patients was noted, compared with controls ($t = 5.31$, $P = 0.07$). Immunoreactive-CBG (IR-CBG) levels were higher in Serine/Alanine (Ser/Ala) than Ala/Ala subjects and higher again in Ser/Ser subjects, this effect was strongest in controls; Ser/Ser: 46.1 ± 1.8 (n = 31, $P = 0.03$) vs. Ser/Ala: 42.4 ± 1.0 (n = 56, $P = 0.05$) vs. Ala/Ala: 40.8 ± 1.7 $\frac{1}{4}$ g/mL (n = 21). Despite higher CBG levels, there was a nonsignificant trend toward lower total and free plasma cortisol in serine allele positive patients, total cortisol: Ser/Ser: 13.3 ± 1.4 (n = 34) vs. Ser/Ala: 14.0 ± 0.7 (n = 66) vs. Ala/Ala: 15.4 ± 1.0 (n = 23). Homozygosity for the serine allele of the CBG gene may predispose to CFS, perhaps due to an effect on hypothalamic-pituitary-adrenal axis function related to altered CBG-cortisol transport function or immune-cortisol interactions.

Roberts A.D.L., Wessely S., Chalder T., Papadopoulos A., Cleare A.J.

Salivary cortisol response to awakening in chronic fatigue syndrome

2004 British Journal of Psychiatry 184 (FEB.); 136 – 141

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Background: There is accumulating evidence of hypothalamic-pituitary- adrenal (HPA) axis disturbances in chronic fatigue syndrome (CFS). The salivary cortisol response to awakening has been described recently as a non-invasive test of the capacity of the HPA axis to respond to stress. The results of this test correlate closely with those of more invasive dynamic tests reported in the literature; furthermore, it can be undertaken in a naturalistic setting. Aims: To assess the HPA axis using the salivary cortisol response to awakening in CFS. Method: We measured salivary cortisol upon awakening and 10, 20, 30 and 60 min afterwards in 56 patients with CFS and 35 healthy volunteers. Results: Patients had a lower cortisol response to awakening, measured by the area under the curve. Conclusions: This naturalistic test of the HPA axis response to stress showed impaired HPA axis function in CFS.

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Elevated levels of some neuroactive progesterone metabolites, particularly isopregnanolone, in women with chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-0242321131&partnerID=40>

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Chronic fatigue syndrome (CFS) is a controversial entity whose cause is unknown. In this study we have explored the possibility that progesterone metabolites may be involved. Plasma levels of the progesterone precursor pregnenolone, progesterone itself, and five ring A-reduced metabolites of progesterone were measured in 20 women with CFS and in 13 age-matched controls. To minimize the contribution of the ovary, women were either post-menopausal or in the follicular phase of the menstrual cycle (day 4-8), and progesterone levels were all well within the expected range (≈ 3.5 nmol/l). Mean values for progesterone and all of its metabolites were higher in CFS patients, the most marked being a 2.3-fold elevation in isopregnanolone ($3\beta^2,5\alpha$ -tetrahydroprogesterone; $p \approx 0.001$). Progesterone levels were correlated with those of its metabolites, but even after controlling for progesterone by ANCOVA, isopregnanolone levels were still elevated ($p \approx 0.001$). These elevated levels of isopregnanolone could not be attributed to medications (antidepressants and anxiolytics). When the CFS patients were divided into two groups according to their Hamilton depression scale ratings, mean ($\bar{A} \pm SD$) isopregnanolone levels were higher ($274 \bar{A} \pm 160$ vs $197 \bar{A} \pm 119$ pmol/l) in the less depressed group (ratings 2-14) than in the more depressed group (ratings 17-28), although this difference did not reach significance. Progesterone levels were negatively correlated with Hamilton depression rating scores ($r = -0.56$; $p < 0.01$). These results suggest that increases in ring A-reduced progesterone metabolites, particularly isopregnanolone, are associated with CFS, and that the pathophysiology of CFS is unlikely to be due to depression. © 2003 Elsevier Ltd. All rights reserved.

Gur A., Cevik R., Nas K., Colpan L., Sarac S.

Cortisol and hypothalamic-pituitary-gonadal axis hormones in follicular-phase women with fibromyalgia and chronic fatigue syndrome and effect of depressive symptoms on these hormones.

2004 Arthritis research & therapy 6 (3)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-12344281899&partnerID=40>

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We investigated abnormalities of the hypothalamic-pituitary-gonadal axis and cortisol concentrations in women with fibromyalgia and chronic fatigue syndrome (CFS) who were in the follicular phase of their menstrual cycle, and whether their scores for depressive symptoms were related to levels of these hormones. A total of 176 subjects participated - 46 healthy volunteers, 68 patients with fibromyalgia, and 62 patients with CFS. We examined concentrations of follicle-stimulating hormone, luteinizing hormone (LH), estradiol, progesterone, prolactin, and cortisol. Depressive symptoms were assessed using the Beck Depression Inventory (BDI). Cortisol levels were significantly lower in patients with fibromyalgia or CFS than in healthy controls ($P < 0.05$); there were no significant differences in other hormone levels between the three groups. Fibromyalgia patients with high BDI scores had significantly lower cortisol levels than controls ($P < 0.05$), and so did CFS patients, regardless of their BDI scores ($P < 0.05$). Among patients without depressive symptoms, cortisol levels were lower in CFS than in fibromyalgia ($P < 0.05$). Our study suggests that in spite of low morning cortisol concentrations, the only abnormalities in hypothalamic-pituitary-gonadal axis hormones among follicular-phase women with fibromyalgia or CFS are those of LH levels in fibromyalgia patients with a low BDI score. Depression may lower cortisol and LH levels, or, alternatively, low morning cortisol may be a biological factor that contributes to depressive symptoms in fibromyalgia. These parameters therefore must be taken into account in future investigations.

Glass J.M., Lyden A.K., Petzke F., Stein P., Whalen G., Ambrose K., Chrousos G., Clauw D.J.
The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals

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Objective Abnormalities of the biological stress response (hypothalamic-pituitary-adrenal axis and the autonomic nervous system) have been identified in both fibromyalgia (FM) and chronic fatigue syndrome (CFS). Although these changes have been considered to be partly responsible for symptom expression, we examine an alternative hypothesis that these HPA and autonomic changes can be found in subsets of healthy individuals in the general population who may be at risk of developing these conditions. Exposure to "stressors" (e.g., infections, trauma, etc.) may lead to symptom expression (pain, fatigue, and other somatic symptoms) in part by precipitating lifestyle changes. In particular, we focus on the effect of deprivation of routine aerobic exercise on the development of somatic symptoms. Methods Eighteen regularly exercising (≈ 4 h/week) asymptomatic, healthy adults refrained from physical activity for 1 week. We predicted that a subset of these individuals would develop symptoms of FM/CFS with exercise deprivation, and this manuscript focuses on the baseline HPA axis, immune, and autonomic function measures that may

predict the development of symptoms. Results Eight of the subjects reported a 10% increase in one or more symptoms (pain, fatigue, mood) after 1 week of exercise deprivation. These symptomatic subjects had lower HPA axis (baseline cortisol prior to VO2max testing), immune (NK cell responsiveness to venipuncture), and autonomic function (measured by heart rate variability) at baseline (prior to cessation of exercise) when compared to the subjects who did not develop symptoms. Conclusions A subset of subjects developed symptoms of pain, fatigue, or mood changes after exercise deprivation. This cohort was different from the individuals who did not develop symptoms in baseline measures of HPA axis, immune, and autonomic function. We speculate that a subset of healthy individuals who have hypoactive function of the biological stress response systems unknowingly exercise regularly to augment the function of these systems and thus suppress symptoms. These individuals may be at risk for developing chronic multisymptom illnesses (CMI) (e.g., FM or CFS among others) when a "stressor" leads to lifestyle changes that disrupt regular exercise. © 2004 Elsevier Inc. All rights reserved.

Gaab J., Engert V., Heitz V., Schad T., Schurmeyer T.H., Ehlert U.
Associations between neuroendocrine responses to the Insulin Tolerance Test and patient characteristics in chronic fatigue syndrome

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Objective Subtle dysregulations of the hypothalamic-pituitary-adrenal (HPA) axis have been proposed as an underlying pathophysiological mechanism in chronic fatigue syndrome (CFS). This study attempted to assess the relationship between patient characteristics and HPA axis functioning using a neuroendocrine challenge test. Method A test battery designed to assess different dimensions of CFS was given to 18 CFS patients and 17 controls. To evaluate the integrity of the HPA axis, the Insulin Tolerance Test (ITT), a centrally acting neuroendocrine challenge test, was performed on patients and controls. ACTH, salivary free cortisol and total plasma cortisol levels were assessed as a measure of the HPA axis stress response. Correlations of patient characteristics were calculated with integrated responses for all endocrine parameters. Results CFS patients had a significantly reduced area under the ACTH response curve (AUC) in the ITT. The AUC was significantly associated with the duration of CFS symptoms ($r=-.592$, $P=.005$) and the severity of fatigue symptomatology ($r=-.41$, $P=.045$). In addition, duration of CFS was correlated with the severity of fatigue symptoms ($r=.38$, $P=.045$). Similar associations were not observed for cortisol parameters. Conclusion It has been postulated that neuroendocrine dysregulations observed in CFS are of an acquired nature. The results of a strong association between the integrated ACTH response and the duration of CFS emphasizes the need to consider factors known to be risk factors for the chronicity of CFS symptoms, such as profound inactivity, deconditioning and sleep abnormalities, as possible candidates for secondary causes of neuroendocrine dysregulations in CFS. © 2004 Elsevier Inc. All rights reserved.

Crofford L.J., Young E.A., Engleberg N.C., Korszun A., Brucksch C.B., McClure L.A., Brown M.B., Demitrack M.A.

Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-2442432182&partnerID=40>

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The objective of this study was to evaluate and compare the basal circadian and pulsatile architecture of the HPA axis in groups of patients with FMS, CFS, or both syndromes with individually matched control groups. Forty patients with either FMS (n=13), FMS and CFS (n=12), or CFS (n=15) were matched by age (18-65), sex, and menstrual status to healthy controls. Subjects were excluded if they met criteria for major Axis I psychiatric disorders by structured clinical interview (SCID). Subjects were admitted to the General Clinical Research Center where meals and activities were standardized. Blood was collected from an intravenous line every 10min over 24h for analysis of ACTH and cortisol. Samples were evaluable for ACTH in 36 subject pairs and for cortisol in 37 subject pairs. There was a significant delay in the rate of decline from acrophase to nadir for cortisol levels in patients with FMS (P<.01). Elevation of cortisol in the late evening quiescent period was evident in half of the FMS patients compared with their control group, while cortisol levels were numerically, but not significantly, lower in the overnight period in patients with CFS compared with their control group. Pulsatility analyses did not reveal statistically significant differences between patient and control groups. We conclude that the pattern of differences for basal circadian architecture of HPA axis hormones differs between patients with FMS and CFS compared to their matched control groups. The abnormalities in FMS patients are consistent with loss of HPA axis resiliency. © 2004 Elsevier Inc. All rights reserved.

Cleare A.J., O'Keane V., Miell J.P.

Levels of DHEA and DHEAS and responses to CRH stimulation and hydrocortisone treatment in chronic fatigue syndrome

2004 Psychoneuroendocrinology 29 (6); 724 – 732

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1942445189&partnerID=40>

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Background: An association between chronic fatigue syndrome (CFS) and abnormalities of the hypothalamo-pituitary-adrenal axis has been described, and other adrenal steroid abnormalities have been suggested. Dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S), apart from being a precursor of sex steroids, have other functions associated with memory, depression and sleep. It has been suggested that CFS may be associated with a state of relative DHEA(-S) deficiency. Therefore we investigated basal levels of DHEA(-S), the cortisol/DHEA molar ratio and the responsiveness of DHEA to stimulation by corticotrophin-releasing hormone (CRH). Recent studies have also suggested that low dose hydrocortisone may be effective at reducing fatigue in CFS. We therefore also assessed these parameters prior to and following treatment with low dose oral hydrocortisone. Methods: Basal levels of serum DHEA, DHEAS and cortisol were measured in 16 patients with CFS without depression and in 16 controls matched for age, gender, weight, body mass index and menstrual history. CRH tests (1 ¼g/kg IV) were carried out on all subjects and DHEA measured at 0, +30 and +90 min. In the patient group, CRH tests were repeated on two further occasions following treatment with hydrocortisone (5 or 10 mg, PO) or placebo for 1 month

each in a double-blind cross over study protocol. Results: Basal levels of DHEA were higher in the patient, compared to the control, group (14.1 ± 2.2 vs. 9.0 ± 0.90 ng/ml, $P=0.04$), while levels of DHEAS in patients (288.7 ± 35.4 μ g/dl) were not different from controls (293.7 ± 53.8 , $P=NS$). Higher DHEA levels were correlated with higher disability scores. Basal cortisol levels were higher in patients, and consequently the cortisol/DHEA molar ratio did not differ between patients and controls. Levels of DHEA (8.9 ± 0.97 ng/ml, $P=0.015$) and DHEAS (233.4 ± 41.6 μ g/dl, $P=0.03$) were lower in patients following treatment with hydrocortisone. There was a rise in DHEA responsiveness to CRH in the patients after treatment but this did not attain significance (AUC c: 2.5 ± 1.7 ng/ml h pre-treatment vs. 6.4 ± 1.2 ng/ml h post-hydrocortisone, $P=0.053$). However, those patients who responded fully to hydrocortisone in terms of reduced fatigue scores did show a significantly increased DHEA responsiveness to CRH (AUCc: -1.4 ± 2.5 ng/ml h at baseline, 5.0 ± 1.2 ng/ml h after active treatment, $P=0.029$). Conclusions: DHEA levels are raised in CFS and correlate with the degree of self-reported disability. Hydrocortisone therapy leads to a reduction in these levels towards normal, and an increased DHEA response to CRH, most marked in those who show a clinical response to this therapy. © 2003 Elsevier Ltd. All rights reserved.

Cevik R., Gur A., Acar S., Nas K., Sarac A.J.

Hypothalamic-pituitary-gonadal axis hormones and cortisol in both menstrual phases of women with chronic fatigue syndrome and effect of depressive mood on these hormones

2004 BMC Musculoskeletal Disorders 5

<http://www.scopus.com/inward/record.url?eid=2-s2.0-12344256081&partnerID=40>

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Background: Chronic fatigue syndrome (CFS) is a disease which defined as medically unexplained, disabling fatigue of 6 months or more duration and often accompanied by several of a long list of physical complaints. We aimed to investigate abnormalities of hypothalamic-pituitary-gonadal (HPG) axis hormones and cortisol concentrations in premenopausal women with CFS and find out effects of depression rate on these hormones. Methods: We examined follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone and cortisol concentrations in 43 premenopausal women (mean age: 32.86 ± 7.11) with CFS and compared matched 35 healthy controls (mean age: 31.14 ± 6.19). Patients were divided according to menstrual cycle phases (follicular and luteal) and compared with matched phase controls. Depression rate was assessed by Beck Depression Inventory (BDI), and patients with high BDI scores were compared to patients with low BDI scores. Results: There were no significant differences in FSH, LH, estradiol and progesterone levels in both of menstrual phases of patients versus controls. Cortisol levels were significantly lower in patients compared to controls. There were no significant differences in all hormone levels in patients with high depression scores versus patients with low depression scores. Conclusion: In spite of high depression rate, low cortisol concentration and normal HPG axis hormones of both menstrual phases are detected in premenopausal women with CFS. There is no differentiation between patients with high and low depression rate in all hormone levels. Depression condition of CFS may be different from classical depression and evaluation of HPG and HPA axis should be performed for understanding of pathophysiology of CFS and planning of treatment. © 2004 Cevik et al; licensee BioMed Central Ltd.

Neuropsychology

Schrijvers D., Van Den Eede F., Maas Y., Cosyns P., Hulstijn W., Sabbe B.G.C.
Psychomotor functioning in chronic fatigue syndrome and major depressive disorder: A comparative study

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Background: Studies comparing chronic fatigue syndrome (CFS) and major depressive disorder (MDD) reported similarities as well as differences between the two disorders. However, whereas psychomotor symptoms have been studied extensively in MDD, such research in CFS is more limited. Moreover, the few studies that compared cognitive and motor performance in MDD and CFS yielded inconsistent results. This study hence directly compares fine psychomotor functioning in both syndromes. Methods: Thirty-eight patients diagnosed with CFS without a current major depressive episode (MDE), 32 MDD patients with a current MDE and 38 healthy controls performed two computerized copying tasks differing in complexity: a line-copying task that mainly requires motor effort and a figure-copying task requiring additional cognitive efforts. All participants were female. A multivariate general linear model was used to compute group differences. Result: Overall, both patient groups performed more slowly than the controls. Compared to CFS patients, patients with MDD needed significantly more time to copy the single lines but no such between-group performance difference was observed for the figure reproductions. In this latter copying task, the increasing complexity of the figures resulted in prolonged reaction times for all three participant groups with the effect being larger and the magnitude similar for the two patient groups. Limitations: All patients were female and most were on psychotropic medication. Conclusions: Both the MDD and CFS patients tested demonstrated an overall fine motor slowing, with the motor component being more affected in the MDD patients than in the CFS patients while both patient groups showed similar cognitive impairments. © 2008 Elsevier B.V. All rights reserved.

Nater U.M., Lin J.M., Maloney E.M., Jones J.F., Tian H., Boneva R.S., Raison C.L., Reeves W.C., Heim C.

Psychiatric comorbidity in persons with chronic fatigue syndrome identified from the Georgia population.

2009 Psychosomatic medicine 71 (5); 557 – 565

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650360452&partnerID=40>

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OBJECTIVE: To compare the prevalence of psychiatric disorders in persons with chronic fatigue syndrome (CFS) identified from the general population and a chronically ill group of people presenting with subsyndromic CFS-like illness ("insufficient symptoms or fatigue" (ISF)). Previous studies in CFS patients from primary and tertiary care clinics have found high rates of psychiatric disturbance, but this may reflect referral bias rather than true patterns of comorbidity with CFS. METHODS: We used random digit dialing to identify unwell individuals. A detailed telephone interview identified those with CFS-like illness. These individuals participated in a 1-day clinical evaluation to confirm CFS or ISF status. We identified 113 cases of CFS and 264 persons with ISF. To identify current and lifetime psychiatric disorders, participants completed the Structured Clinical Interview for DSM-IV. RESULTS: Sixty-four persons (57%) with CFS had at least one current psychiatric diagnosis, in contrast to 118 persons (45%) with ISF. One hundred one persons (89%)

with CFS had at least one lifetime psychiatric diagnosis compared with 208 persons (79%) with ISF. Of note, only 11 persons (9.8%) with CFS and 25 persons (9.5%) with ISF reported having seen a mental healthcare specialist during the past 6 months. CONCLUSIONS: Our findings indicate that current and lifetime psychiatric disorders commonly accompany CFS in the general population. Most CFS cases with comorbid psychiatric conditions had not sought appropriate help during the past 6 months. These results demonstrate an urgent need to address psychiatric disorders in the clinical care of CFS cases.

Matsuda Y., Matsui T., Kataoka K., Fukada R., Fukuda S., Kuratsune H., Tajima S., Yamaguti K., Kato Y.H., Kiriike N.

A two-year follow-up study of chronic fatigue syndrome comorbid with psychiatric disorders

2009 Psychiatry and Clinical Neurosciences 63 (3); 365 – 373

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65649098065&partnerID=40>

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Chronic fatigue syndrome patients often have comorbid psychiatric disorders such as major depressive disorders and anxiety disorders. However, the outcomes of chronic fatigue syndrome and the comorbid psychiatric disorders and the interactions between them are unknown. Therefore, a two-year prospective follow-up study was carried out on chronic fatigue syndrome patients with comorbid psychiatric disorders. Methods: A total of 155 patients who met the Japanese case definition of chronic fatigue syndrome were enrolled in this study. Comorbid psychiatric disorders were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria. Patients with comorbid psychiatric disorders received psychiatric treatment in addition to medical therapy for chronic fatigue syndrome. Seventy patients participated in a follow-up interview approximately 24 months later. Results: Of the 70 patients with chronic fatigue syndrome, 33 patients were diagnosed as having comorbid psychiatric disorders including 18 major depressive disorders. Sixteen patients with psychiatric disorders and eight patients with major depressive disorders did not fulfill the criteria of any psychiatric disorders at the follow up. As for chronic fatigue syndrome, nine out of the 70 patients had recovered at the follow up. There is no significant influence of comorbid psychiatric disorders on the outcome of chronic fatigue syndrome. Conclusions: Chronic fatigue syndrome patients have a relatively high prevalence of comorbid psychiatric disorders, especially major depressive disorders. The outcomes of chronic fatigue syndrome and psychiatric disorders are independent. Therefore treatment of comorbid psychiatric disorders is necessary in addition to the medical treatment given for chronic fatigue syndrome. © 2009 Japanese Society of Psychiatry and Neurology.

Lyle N., Gomes A., Sur T., Munshi S., Paul S., Chatterjee S., Bhattacharyya D.

The role of antioxidant properties of *Nardostachys jatamansi* in alleviation of the symptoms of the chronic fatigue syndrome

2009 Behavioural Brain Research 202 (2); 285 – 290

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65649119734&partnerID=40>

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An experimental model of chronic fatigue syndrome (CFS) is utilized for evaluation of antidepressant, anti-stress effects, wherein the rat is forced to swim in water for 15 min/day on 21

consecutive days. Rats were divided into stressed control, stressed plus standard drug (Panax ginseng) and stressed plus 200 and 500 mg/kg of test drug, i.e., Nardostachys jatamansi extract (NJE) given orally. The immobility during each 5 min periods of 0-5, 5-10 and 10-15 min of stress were noted. Similarly the climbing (struggling) behaviour was noted in the above four groups of rats in intervals of 5 min. The locomotor activity and also the anxiety state in animals were evaluated in an elevated plus maze after CFS in all the four groups. There was a significant increase in despair behaviour and anxiety in stressed control animals on successive days of CFS. Locomotor activity gradually decreased in stressed control group. Treatment with NJE (200 and 500 mg/kg) significantly reversed both paradigms. Biochemical analysis showed that CFS significantly increased lipid peroxidation, nitrite and superoxide dismutase levels and decreased catalase level in rat brain. Administration of NJE (200 and 500 mg/kg) tended to normalize both augmented lipid peroxidation, nitrite, superoxide dismutase activities and catalase level significantly. NJE per se has an antioxidant effect. The results indicate that CFS may lead to oxidative stress, which is mitigated by NJE and so its antioxidant property may be responsible for anti-stress effect of NJE. © 2009 Elsevier B.V. All rights reserved.

Godfrey E., Cleare A., Coddington A., Roberts A., Weinman J., Chalder T.
Chronic fatigue syndrome in adolescents: Do parental expectations of their child's intellectual ability match the child's ability?

2009 Journal of Psychosomatic Research 67 (2); 165 – 168

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650429923&partnerID=40>

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Objective: This cross-sectional study aimed to measure the discrepancy between actual and perceived IQ in a sample of adolescents with CFS compared to healthy controls. We hypothesized that adolescents with CFS and their parent would have higher expectations of the adolescent's intellectual ability than healthy adolescents and their parent. Methods: The sample was 28 CFS patients and 29 healthy controls aged 11-19 years and the parent of each participant. IQ was assessed using the AH4 group test of general intelligence and a self-rating scale which measured perceived IQ. Results: Parents' perceptions of their children's IQ were significantly higher for individuals with CFS than healthy controls. Conclusions: High expectations may need to be addressed within the context of treatment. © 2009 Elsevier Inc. All rights reserved.

Crawley E., Hunt L., Stallard P.
Anxiety in children with CFS/ME

2009 European Child and Adolescent Psychiatry 1 (7)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65649093386&partnerID=40>

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Anxiety symptoms are commonly described in children with chronic fatigue syndrome or myalgic encephalopathy (CFS/ME) but to date there has been little information on the type of anxiety children experience or the relationship between anxiety and school attendance, disability or fatigue. The aim of this study was to first describe the prevalence and type of anxiety symptoms in children with CFS/ME compared with a normal European population, and secondly to investigate the association of anxiety symptoms with age, gender, school attendance, fatigue, and physical function in paediatric CFS/ME. Data were prospectively collected on children and young people with CFS/ME referred to a large specialist CFS/ME service. One hundred and sixty-four children with CFS/ME had

complete data for the Spence Children's Anxiety Scale. Teenage girls had the highest rates of total anxiety symptoms with 38% (95% CI 27-49) over the cut off (top 10% of normal European population) and significantly higher rates of symptoms in each subscale. Younger girls were more likely to score over the cut off in separation anxiety (37%, 19-40) and social phobia (39%, 25-47). There was no evidence of association between total anxiety symptoms and: time at school, time to assessment, pain or age. Associations with fatigue and physical function were attenuated when adjusted for other variables. Although anxiety symptoms are high in CFS/ME, particularly in teenage girls, it does not appear to be associated with school attendance or other measures of disability. Separation anxiety and social phobia were the most clearly elevated in paediatric CFS/ME. © 2009 Springer-Verlag.

Courjaret J., Schotte C.K.W., Wijnants H., Moorkens G., Cosyns P.
Chronic fatigue syndrome and DSM-IV personality disorders

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-57349087052&partnerID=40>

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Objective: Personality is an important factor in the research of the chronic fatigue syndrome (CFS). Although some studies report a high rate of personality disorders-around the 40% level-in samples of patients with CFS, the generalizability of these findings can be questioned. The present study evaluates the prevalence of Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) personality disorders in a sample of female CFS patients and in two control groups. Method: The ADP-IV questionnaire (Assessment of DSM Personality Disorders IV) was used to assess the DSM-IV-TR personality disorders at a dimensional and categorical level in a sample of 50 female CFS patients and in two matched control samples of Flemish civilians (n=50) and psychiatric patients (n=50). Results: The results indicate a striking lack of statistical significant differences between the CFS sample and the Flemish control group at the level of dimensional Trait scores, number of criteria, and prevalence rates of personality disorder diagnoses. Unsurprisingly, higher scores at these levels were obtained within the psychiatric sample. The prevalence of an Axis II disorder was 12% in the Flemish and CFS samples, whereas the psychiatric sample obtained a prevalence of 54%. Conclusion: The prominent absence of any significant difference in personality disorder characteristics between the female Flemish general population and the CFS samples seems to suggest only a minor etiological role for personality pathology, as defined by the DSM-IV Axis II, within CFS. © 2009 Elsevier Inc. All rights reserved.

Claes S.J., Campen E.V., Van Den Eede F., Moorkens G., Schotte C., Schacht R., Sabbe B.G.C., Cosyns P.

Use of the temperament and character inventory (tci) for assessment of personality in chronic fatigue syndrome

2009 Psychosomatics 50 (2); 147 - 154

<http://www.scopus.com/inward/record.url?eid=2-s2.0-66849091697&partnerID=40>

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Background: Chronic fatigue syndrome (CFS) is characterized by severe and prolonged fatigue, along with a set of nonspecific symptoms and signs, such as sore throat, muscle pain, headaches, and difficulties with concentration or memory. Objective: The study examined whether CFS is associated with specific dimensions of Cloninger's psychobiological model of personality. Method: Personality profiles were compared between 38 CFS patients and 42 control subjects by means of

the Temperament and Character Inventory (TCI). Results: The CFS group showed significantly higher scores on Harm-Avoidance and Persistence. Conclusion: The current study shows a significant association between specific personality characteristics and CFS. These personality traits may be implicated in the onset and/or perpetuation of CFS and may be a productive focus for psychotherapy. © 2009 The Academy of Psychosomatic Medicine.

Attree E.A., Dancey C.P., Pope A.L.

An assessment of prospective memory retrieval in women with chronic fatigue syndrome using a virtual-reality environment: An initial study

2009 Cyberpsychology and Behavior 12 (4); 379 – 385

<http://www.scopus.com/inward/record.url?eid=2-s2.0-68149169559&partnerID=40>

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People with chronic fatigue syndrome (CFS) have increased rates of depression, anxiety, and illness intrusiveness; they may also suffer from cognitive problems such as retrospective memory (RM) deficits and concentration difficulties that can stem from diminished information-processing capability. We predicted that this diminished capacity may also lead to deficits in other cognitive functions, such as prospective memory (ProM). Event-, time-, and activity-based ProM was assessed in 11 women with CFS and 12 healthy women using a computer-generated virtual environment (VE). RM was assessed using a free-recall test, and subjective assessment of both ProM and RM was assessed by questionnaire. Groups were equivalent in age and measures of IQ. People with CFS performed slightly worse than healthy controls on both the event- and time-based ProM measures, although these were not statistically significant. However, the CFS group performed significantly worse than the healthy controls on both the free recall-task and on subjective assessment of both RM and ProM. Women with CFS do have some subtle decrements in memory, particularly RM. However, it is possible that the decrements found in the present sample would be greater in real life. Further studies utilizing both healthy controls and illness controls are now needed to ascertain how sensitive the VE measure is and to inform the development of tasks in the VE that place progressively increasing demands on working memory capacity. © Copyright 2009, Mary Ann Liebert, Inc.

Watanabe N., Stewart R., Jenkins R., Bhugra D.K., Furukawa T.A.

The epidemiology of chronic fatigue, physical illness, and symptoms of common mental disorders: A cross-sectional survey from the second British National Survey of Psychiatric Morbidity

2008 Journal of Psychosomatic Research 64 (4); 357 – 362

<http://www.scopus.com/inward/record.url?eid=2-s2.0-40949130369&partnerID=40>

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Objective: The study aimed to describe the prevalence of chronic fatigue in the general population and to investigate the extent to which its association with physical illness was independent of other symptoms of common mental disorders. Methods: Data from the second British National Survey of Psychiatric Morbidity (2000) were analyzed. The survey covered people aged 16 to 74 years living in private households. Chronic fatigue (significant reported fatigue lasting 6 months or more) was ascertained using the revised Clinical Interview Schedule. Information on reported physical illness and sociodemographic factors was considered. Psychiatric symptoms were also assessed using the revised Clinical Interview Schedule. Results: The prevalence of chronic fatigue was 15.0%, and this showed a significant association with the number of reported physical illnesses (odds ratio [OR] per reported illness, 1.79; 95% confidence interval, 1.68-1.90). It was higher in midlife, in women, in

participants with less skilled occupations, and in those with lower educational attainment. Chronic fatigue was strongly associated with the presence of depressive symptoms (OR, 5.37), anxiety-related symptoms (OR, 4.66), and with sleep complaints (OR, 4.41). After adjustment for all sociodemographic and psychiatric factors, the number of reported physical illnesses was less strongly but still significantly associated with chronic fatigue (OR, 1.51; 1.39-1.63). Conclusion: Physical illness is strongly associated with chronic fatigue. Symptoms of common mental disorders are also associated with chronic fatigue, but the association between physical illness and chronic fatigue is evident even after adjusting for psychiatric symptoms. The assessment of physically ill people should include chronic fatigue and psychiatric symptoms. © 2008 Elsevier Inc. All rights reserved.

Sohl S.J., Friedberg F.

Memory for fatigue in chronic fatigue syndrome: Relationships to fatigue variability, catastrophizing, and negative affect

2008 Behavioral Medicine 34 (1); 29 - 35

<http://www.scopus.com/inward/record.url?eid=2-s2.0-42549143903&partnerID=40>

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Fatigue in chronic fatigue syndrome (CFS) is usually assessed with retrospective measures rather than real-time momentary symptom assessments. In this study, the authors hypothesized that in participants with CFS, discrepancies between recalled and momentary fatigue would be related to catastrophizing, anxiety, and depression and to variability of momentary fatigue. They also expected that catastrophizing, anxiety, and depression would be associated with momentary fatigue. The authors asked 53 adults with CFS to carry electronic diaries for 3 weeks and record their experiences of momentary fatigue. The authors assessed participants fatigue recall with weekly ratings and administered questionnaires for catastrophizing, depression, and anxiety. Recall discrepancy was significantly related to the variability of momentary fatigue. In addition, catastrophizing, depression, and momentary fatigue were all significantly related to recall discrepancy. Catastrophizing, depression, anxiety, and momentary negative affect were all significantly associated with momentary fatigue. The findings suggest that momentary fatigue in patients with CFS is related to modifiable psychological factors. Copyright © 2008 Heldref Publications.

Majer M., Welberg L.A., Capuron L., Miller A.H., Pagnoni G., Reeves W.C.

Neuropsychological performance in persons with chronic fatigue syndrome: results from a population-based study.

2008 Psychosomatic medicine 70 (7); 829 - 836

<http://www.scopus.com/inward/record.url?eid=2-s2.0-58149386291&partnerID=40>

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OBJECTIVE: To examine the neuropsychological function characterized in subjects with chronic fatigue syndrome (CFS) at the same time controlling for relevant confounding factors. CFS is associated with symptoms of neuropsychological dysfunction. Objective measures of neuropsychological performance have yielded inconsistent results possibly due to sample selection bias, diagnostic heterogeneity, comorbid psychiatric disorders, and medication usage. **METHOD:** CFS subjects (n = 58) and well controls (n = 104) from a population-based sample were evaluated, using standardized symptom severity criteria. Subjects who had major psychiatric disorders or took medications known to influence cognition were excluded. Neuropsychological function was measured using the Cambridge Neuropsychological Test Automated Battery (CANTAB). **RESULTS:** Compared

with controls, CFS subjects exhibited significant decreases in motor speed as measured in the simple and five-choice movement segments of the CANTAB reaction time task. CFS subjects also exhibited alterations in working memory as manifested by a less efficient search strategy on the spatial working memory task, fewer % correct responses on the spatial recognition task, and prolonged latency to a correct response on the pattern recognition task. A significantly higher percentage of CFS subjects versus controls exhibited evidence of neuropsychological impairment (defined by performance 1 standard deviation below the CANTAB normative mean) in tasks of motor speed and spatial working memory. Impairment in CFS subjects versus control subjects ranged from 20% versus 4.8% in five-choice movement time ($p = .002$) to 27.8% versus 10.6% in search strategy on the spatial working memory task ($p = .006$). CONCLUSIONS: These results confirm and quantify alterations in motor speed and working memory in CFS subjects independent of comorbid psychiatric disease and medication usage.

Hou R., Moss-Morris R., Bradley B.P., Peveler R., Mogg K.
Attentional bias towards health-threat information in chronic fatigue syndrome

2008 Journal of Psychosomatic Research 65 (1); 47 – 50

<http://www.scopus.com/inward/record.url?eid=2-s2.0-45449095013&partnerID=40>

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Objective: To investigate whether individuals with chronic fatigue syndrome (CFS) show an attentional bias towards health-threat information. Methods: Attentional bias (AB) was assessed in individuals with CFS and healthy controls using a visual probe task which presented health-threat and neutral words and pictures for 500 ms. Self-report questionnaires were used to assess CFS symptoms, depression, anxiety, and social desirability. Results: Compared to a healthy control group, the CFS group showed an enhanced AB towards health-threat stimuli relative to neutral stimuli. The AB was not influenced by the type of stimulus (pictures vs. words). Conclusion: The finding of an AB towards health-threat information in individuals with CFS is supportive of models of CFS which underlie cognitive behavior therapy. © 2008 Elsevier Inc. All rights reserved.

Harvey S.B., Wadsworth M., Wessely S., Hotopf M.
The relationship between prior psychiatric disorder and chronic fatigue: Evidence from a national birth cohort study

2008 Psychological Medicine 38 (7); 933 - 940

<http://www.scopus.com/inward/record.url?eid=2-s2.0-44449151576&partnerID=40>

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Background. Increased rates of psychiatric disorder have previously been reported in those diagnosed with chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME), although the direction of causation in this relationship has not been established. We aimed to test the hypothesis that individuals with self-reported CFS/ME have increased levels of psychiatric disorder prior to the onset of their fatigue symptoms. Method. A total of 5362 participants were prospectively followed with various measures of personality, psychiatric disorder and fatigue levels collected over the first 43 years of their life. CFS/ME was identified through self-report during a semi-structured interview at age 53 years. Results: Thirty-four (1.1%) of the 3035 subjects assessed at age 53 years reported a diagnosis of CFS/ME. CFS/ME was more common among females, but there was no association between CFS/ME and either social class, social mobility or educational level. Those with psychiatric illness between the ages of 15 and 36 years were more likely to report CFS/ME later in life with an odds ratio (OR, adjusted for sex) of 2.65 [95% confidence interval (CI) 1.26-5.57, $p=0.01$].

Increased levels of psychiatric illness, in particular depression and anxiety, were present prior to the occurrence of fatigue symptoms. There was a dose-response relationship between the severity of psychiatric symptoms and the likelihood of later CFS/ME. Personality factors were not associated with a self-reported diagnosis of CFS/ME. Conclusions. This temporal, dose-response relationship suggests that psychiatric disorders, or shared risk factors for psychiatric disorders, are likely to have an aetiological role in some cases of CFS/ME. Copyright © 2007 Cambridge University Press.

Fuller-Thomson E., Nimigon J.

Factors associated with depression among individuals with chronic fatigue syndrome: Findings from a nationally representative survey

2008 Family Practice 25 (6); 414 - 422

<http://www.scopus.com/inward/record.url?eid=2-s2.0-56849131880&partnerID=40>

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Objectives. Most previous research regarding chronic fatigue syndrome (CFS) and depression has relied on clinical samples. The current research determined the prevalence and correlates of depression among individuals with CFS in a community sample. **Methods.** The nationally representative Canadian Community Health Survey, conducted in 2000/2001, included an unweighted sample size of 1045 individuals who reported a diagnosis of CFS and had complete data on depression. Respondents with CFS who were depressed (n = 369) were compared to those who were not depressed (n = 676). Chi-square analyses, t -tests and a logistic regression were conducted. **Results.** Thirty-six per cent of individuals with CFS were depressed. Among individuals with CFS, depression was associated with lower levels of mastery and self-esteem. In the logistic regression analyses, the odds of depression among individuals with CFS were higher for females, younger respondents, those with lower incomes and food insecurity and those whose activities were limited by pain. Two in five depressed individuals had not consulted with any mental health professional in the preceding year. Twenty-two per cent of depressed respondents had seriously considered suicide in the past year. Individuals with CFS who were depressed were particularly heavy users of family physicians, with an average of 11.1 visits annually (95% confidence interval = 10.7, 11.6). **Conclusion.** It is important for clinicians to assess depression and suicidal ideation among their patients with CFS, particularly among females, those reporting moderate to severe pain, low incomes and inadequate social support. © The Author 2008. Published by Oxford University Press. All rights reserved.

Dancey C.P., Friend J.

Symptoms, impairment and illness intrusiveness-their relationship with depression in women with CFS/ME

2008 Psychology and Health 23 (8); 983 - 999

<http://www.scopus.com/inward/record.url?eid=2-s2.0-52949102935&partnerID=40>

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Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is an illness in which physiological and psychological factors are believed to interact to cause and maintain CFS/ME in an individual predisposed to it. The various symptoms and impairments associated with CFS/ME have a large impact on quality of life. The purpose of the present study was to identify the extent to which the core symptoms and impairments associated with CFS/ME relate to depression in women with CFS/ME, and to discover whether these relationships were mediated by illness intrusiveness. CFS/ME was found to be a highly intrusive illness, intruding into more life domains and to a greater degree than other illnesses. The effects of both symptoms and impairment on depression were, in part, mediated by illness intrusiveness. Although symptoms severity and impairment had both direct and

indirect effects on depression, illness intrusiveness was the strongest predictor of depression.

Abdel-Khalek A.M.

Chronic fatigue syndrome and its association with obsession compulsion among a non-clinical sample using questionnaires

2008 Journal of Chronic Fatigue Syndrome 14 (3); 89 – 100

<http://www.scopus.com/inward/record.url?eid=2-s2.0-39749198591&partnerID=40>

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The present study investigated the possible association between the Chronic Fatigue Syndrome (CFS) and Obsession Compulsion (OC). A non-clinical sample of 427 volunteer Kuwaiti male and female college students was recruited. Their ages ranged from 17 to 40 years. They completed the Arabic Scale of CFS (ASCFS) and the Arabic Scale of Obsession Compulsion (ASOC). Both have good reliability and validity. Females had significantly higher mean score on the ASCFS than did their male counterparts. All the intercorrelations between the 20 items as well as the total score of the ASCFS were statistically significant ($p < 0.01$) with the total ASOC score in males and females. It was concluded that there is an obsessive compulsive element in CFS, and both disorders share specific common elements. Copyright © by The Haworth Press, Inc. All rights reserved.

Priebe S., Fakhoury W.K.H., Henningsen P.

Functional incapacity and physical and psychological symptoms: How they interconnect in chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-50549099285&partnerID=40>

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Background: It has been argued that perceived functional incapacity might be a primary characteristic of chronic fatigue syndrome (CFS) and could be explained by physical symptoms. If so, it could be expected to be closely associated with physical, but not psychological symptoms. The study tests this hypothesis. Sampling and Methods: The sample consisted of 73 patients, with a diagnosis of CFS according to the Oxford criteria, randomly selected from clinics in the Departments of Immunology and Psychiatry at St. Bartholomew's Hospital, London. The degree of fatigue experienced by patients was assessed using the Chalder Fatigue Questionnaire and a visual analogue scale. Self-rated instruments were used to measure physical and social functioning, quality of life, and physical and psychological symptoms. Results: Principal-component analysis of all scale scores revealed 2 distinct components, explaining 53% of the total variance. One component was characterized by psychological symptoms and generic quality of life indicators, whilst the other component was made up of physical symptoms, social and physical functioning and indicators of fatigue. Conclusions: The findings suggest that perceived functional incapacity is a primary characteristic of CFS, which is manifested and/or explained by physical symptoms. Copyright © 2008 S. Karger AG.

Young J.L., Redmond J.C.

Fibromyalgia, chronic fatigue, and adult attention deficit hyperactivity disorder in the adult: a case study.

2007 Psychopharmacology bulletin 40 (1); 118 – 126

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34247866344&partnerID=40>

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Adult attention deficit hyperactivity disorder (ADHD) may share common features with fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS). In an outpatient psychiatric clinic, a number of adult patients who presented primarily with symptoms of ADHD, predominately inattentive type, also reported unexplained fatigue, widespread musculoskeletal pain or a pre-existing diagnosis of CFS or FMS. As expected, ADHD pharmacotherapy usually attenuated the core ADHD symptoms of inattention, distractibility, hyperactivity, and impulsivity. Less expected was the observation that some patients also reported amelioration of pain and fatigue symptoms. The utility of ADHD medications in FMS and CFS states may be their innate arousal and enhanced filtering properties. This model supposes that FMS and CFS are central processing problems rather than peripheral disorders of muscles and joints.

van de Putte E.M., Engelbert R.H.H., Kuis W., Kimpen J.L.L., Uiterwaal C.S.P.M.

Alexithymia in adolescents with chronic fatigue syndrome

2007 Journal of Psychosomatic Research 63 (4); 377 – 380

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34648835396&partnerID=40>

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Background: Alexithymia is postulated as an important factor in the development of medically unexplained physical symptoms. Chronic fatigue syndrome (CFS) is presently medically unexplained. The aim of this study was to investigate whether the prevalence of alexithymia was higher in adolescents with CFS compared to healthy adolescents. Comorbidity such as anxiety and depression were analyzed as possible confounding factors. Secondly, alexithymia was investigated as a prognostic factor for the recovery of CFS. Methods: A cross-sectional study was performed among 40 adolescent outpatients diagnosed with CFS and 36 healthy controls. The 20-item Toronto Alexithymia Scale was used to assess all participants for alexithymia. Additionally, all participants completed a number of questionnaires regarding fatigue (Checklist Individual Strength), somatic complaints (Checklist Somatization Inventory), depression (Children's Depression Inventory), and trait anxiety (Spielberger State Trait Anxiety Questionnaire). A follow-up study was performed among the CFS adolescents 1 1/2 years after the initial assessment. Results: CFS adolescents scored higher only on the subscale identifying feelings of the TAS-20 [mean difference after adjustment for depression and anxiety 2.8 (95% CI: 0.6; 4.9)]. Twelve CFS adolescents (30%) fulfilled criteria for alexithymia. This subgroup was characterized by higher scores for depression and anxiety and equal scores for fatigue and somatic complaints. At follow-up, no differences in recovery were established between the alexithymic and nonalexithymic CFS adolescents. Conclusions: Alexithymia neither appears to be a unique correlate of CFS nor to be a prognostic factor for recovery of the CFS illness. © 2007 Elsevier Inc. All rights reserved.

Tomoda A., Mizuno K., Murayama N., Joudoi T., Igasaki T., Miyazaki M., Miike T.
Event-related potentials in Japanese childhood chronic fatigue syndrome

2007 Journal of Pediatric Neurology 5 (3); 199 – 208

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The aim of this study was to investigate cognitive functions such as allocation and information processing in patients with childhood type chronic fatigue syndrome (CCFS) using event-related potentials. A total of 190 healthy children as controls and 414 patients with CCFS participated in this study. Both patients and controls had (i) event-related potentials (including P300, P100, N150 and P200 measurements); (ii) component analysis of electrocardiographic R-R interval to evaluate autonomic function; and (iii) KANA-Pick-out test to evaluate frontal lobe function. The cutoff threshold defining abnormal P300 latency to target stimuli and amplitude to non-target stimuli was set at two standard deviations above the mean values of controls. Forty patients (classified as Type-I) had an abnormally-prolonged P300 latency to target stimuli, and 49 patients (classified as Type-II) had an abnormally-exaggerated P300 amplitude, and the remaining 325 patients whose P300 latency and amplitude ranged below the above-mentioned threshold were classified as Type-III. All patient groups had normal P100, N150 and P200 measurements. Component analysis of electrocardiographic R-R intervals revealed that the power of high-frequency components was lower in all patient groups, compared to controls. The score in KANA-Pick-out test was worse in all patient groups compared to controls; Type-I Group had the worst score and Type-II Group had the best score among the patients. Taken together, we speculate that abnormally-prolonged P300 latency to target stimuli might be associated with learning disability and abnormally-exaggerated P300 amplitude to non-target stimuli might be associated with hypersensitivity such as phobia in patients with CCFS. Psychosomatic symptoms in patients with CCFS might be associated with higher-order level cognitive dysfunction. © 2007 IOS Press. All rights reserved.

Matthews R.M., Komaroff A.L.

Changes in functional status in chronic fatigue syndrome over a decade: Do age and gender matter?

2007 Journal of Chronic Fatigue Syndrome 14 (1); 33 – 42

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34249341716&partnerID=40>

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Objective: Patients with chronic fatigue syndrome (CFS) have substantial deficits in functional capacity, but the course of these deficits over time has not often been studied. This study measured functional capacity on three occasions over a decade, in patients with CFS. Methods: The study was a longitudinal cohort study, and employed the Medical Outcomes Study Short Form-36 (SF-36) instrument to assess physical and mental/emotional functional status. Results: Physical function, as reflected in several different scales, improved modestly but significantly over time, particularly for patients aged 18-60 years and for women. Mental/emotional function was not substantially impaired at the outset of the study, and did not change over time. Conclusion: This study found that physical function tended to improve for many patients over time, despite the fact that they were aging. Physical function did not deteriorate with time. Copyright © by The Haworth Press, Inc. All rights reserved.

Le Bon O., Cappeliez B., Neu D., Stulens L., Hoffmann G., Hansenne M., Lambrecht L., Anseau M., Linkowski P.

Personality profile of patients with chronic fatigue syndrome

2007 Journal of Chronic Fatigue Syndrome 14 (1); 55 – 68

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34249340471&partnerID=40>

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Personality may play a role in the predisposition, the precipitation and/or the maintenance of the CFS. Thirty-six consecutively examined female patients hospitalised for a sleep workup, filled out a Temperament and Character Inventory (TCI) questionnaire. A MANOVA compared the patients with a control group of females matched for age. Significant scores were obtained for dimensions such as Harm Avoidance, Reward Dependence, and Self-Directedness. However, the only subdimension of Harm Avoidance that proved significantly higher in CFS than in controls was "Fatigability," which is likely to overlap with the core CFS symptom. All in all, the personality structure does not appear to play a major role in the CFS. Copyright   by The Haworth Press, Inc. All rights reserved.

Friedberg F., Quick J.

Alexithymia in chronic fatigue syndrome: Associations with momentary, recall, and retrospective measures of somatic complaints and emotions

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33846479378&partnerID=40>

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OBJECTIVE: The relationship between alexithymia and real-time momentary symptom assessments has not been reported. This cross-sectional study hypothesized that alexithymia would be a predictor of somatic symptoms using three different types of symptom measurement (momentary, recall, and retrospective) in the medically unexplained illness of chronic fatigue syndrome (CFS). In addition, it was hypothesized that negative affect would be a significant mediator of the relationship between alexithymia and somatic symptoms. Finally, the relation of alexithymia to physical illness attribution (a CFS illness predictor) was explored. **METHODS:** Participants were 111 adults with CFS. Alexithymia was assessed with the Toronto Alexithymia Scale. Momentary ratings of current symptoms and affect were recorded in electronic diaries carried for 3 weeks. Weekly recall of these momentary reports was also recorded. Retrospective measures included 6-month ratings of fatigue and pain, the Fatigue Severity Scale, the Brief Pain Inventory-Short Form, a CFS symptom measure, the Beck Depression Inventory-II, the Beck Anxiety Inventory, and an illness attribution rating. **RESULTS:** Partial correlations, controlling for age and sex, yielded no significant associations between general or specific forms of alexithymia and momentary ratings of fatigue or pain. On the other hand, a significant association, partially mediated by anxiety scores, was found between a specific form of alexithymia and a retrospective pain measure. Finally, physical illness attribution was not significantly associated with alexithymia. **CONCLUSION:** Based on assessments of real-time and retrospectively measured symptoms, these data provided only modest support for the alexithymia construct as a predictor of somatic symptoms in people with CFS. Copyright   2007 by American Psychosomatic Society.

Claypoole K.H., Noonan C., Mahurin R.K., Goldberg J., Erickson T., Buchwald D.
A Twin Study of Cognitive Function in Chronic Fatigue Syndrome: The Effects of Sudden Illness Onset

2007 *Neuropsychology* 21 (4); 507 - 513

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Variable reports of neuropsychological deficits in individuals with chronic fatigue syndrome (CFS) may, in part, be attributable to methodological limitations. In this study, these limitations were addressed by controlling for genetic and environmental influences and by assessing the effects of comorbid depression and mode of illness onset. Specifically, the researchers conducted a co-twin control study of 22 pairs of monozygotic twins, in which 1 twin met strict criteria for CFS and the co-twin was healthy. Twins underwent a structured psychiatric interview and comprehensive neuropsychological assessment evaluating 6 cognitive domains. Results indicated that twin groups had similar intellectual and visual memory functioning, but fatigued twins exhibited decreases in motor functions ($p = .05$), speed of information processing ($p = .02$), verbal memory ($p = .02$), and executive functioning ($p < .01$). Major depression did not affect neuropsychological functioning among fatigued twins, although twins with sudden illness onset demonstrated slowed information processing compared with those with gradual onset ($p < .01$). Sudden onset CFS was associated with reduced speed of information processing. If confirmed, these findings suggest the need to distinguish illness onset in future CFS studies and may have implications for treatment, cognitive rehabilitation, and disability determination. © 2007 American Psychological Association.

Boiko A.N., Batysheva T.T., Matvievskaya O.V., Manevich T.M., Gusev E.I.
Characteristics of the formation of chronic fatigue syndrome and approaches to its treatment in young patients with focal brain damage

2007 *Neuroscience and Behavioral Physiology* 37 (3); 221 – 228

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33947393986&partnerID=40>

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Chronic fatigue is among the manifestations of focal brain lesions. It is most often encountered in multiple sclerosis (MS) and patients with the sequelae of traumatic, inflammatory, and vascular brain damage (encephalopathies). The aim of the present work was to study the mechanisms of formation of this syndrome in 50 patients with focal brain lesions of different origins (in the inactive stage) and to assess the possibility of correcting it using the combined agent Fezam (2 capsules t.i.d. for one month), which contains piracetam and cinarrizine. In patients with encephalopathies, chronic fatigue syndrome was directly associated with the severity of depression. Patients with MS showed changes in the value-sense sphere. Neuropsychological testing showed that the psychological and personality components played a greater role in the origins of chronic fatigue in patients with encephalopathies than in those with MS. Fezam significantly decreased the severity of chronic fatigue, particularly in patients with MS; in the second group (non-MS patients) this was accompanied by a decrease in the severity of depression. Mild side effects (in six patients 12%) consisted generally of sleep disturbances. These results indicate that Fezam should be used in the treatment of chronic fatigue in patients with focal brain lesions; in encephalopathies it should be combined with psychoactive agents. © Springer Science+Business Media, Inc. 2007.

Bennett B., Goldstein D., Friedlander M., Hickie I., Lloyd A.
The Experience of Cancer-Related Fatigue and Chronic Fatigue Syndrome: A Qualitative and Comparative Study

2007 *Journal of Pain and Symptom Management* 34 (2); 126 – 135

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34547096009&partnerID=40>

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Cancer-related fatigue (CRF) is a common and disabling symptom complex reported by survivors. This study aimed to better understand the manifestations of CRF in women treated for breast cancer, and to compare them with those of women diagnosed with chronic fatigue syndrome (CFS). Women with CRF persisting 6 months after treatment for early stage breast cancer, and women with CFS participated in separate, audiotaped focus groups. Transcripts of the sessions were analyzed using the NUD*IST software, and interpreted using grounded theory. Twenty-eight women participated, 16 with CRF and 12 with CFS. Analysis of transcripts from both groups revealed a similar core set of symptoms, featuring fatigue, neurocognitive difficulties, and mood disturbances. Women with CFS reported additional symptoms including musculoskeletal pain and influenza-like manifestations. Both groups suffered disabling behavioral consequences of the symptom complex. Qualitatively, CRF appears closely related to CFS. These findings raise the emergent hypothesis of a conserved neurobehavioral symptom complex, which results from diverse triggering insults. © 2007 U.S. Cancer Pain Relief Committee.

Yoshiuchi K., Farkas J., Natelson B.H.

Patients with chronic fatigue syndrome have reduced absolute cortical blood flow

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Prior studies on brain blood flow in chronic fatigue syndrome (CFS) did not find consistent results. This may be because they used single-photon emission computed tomography to measure brain blood flow, which could not measure absolute blood flow. Therefore, the aim of this study was to test the hypothesis that patients with CFS have reduced absolute cerebral blood flow. Xenon-computed tomography blood flow studies were done on 25 CFS patients and seven healthy controls. Analyses were done after stratifying the CFS patients based on the presence or absence of a current psychiatric disorder. Flow was diminished in both groups as follows: patients with no current psychiatric disorders had reduced cortical blood flow in the distribution of both right and left middle cerebral arteries ($P < 0.05$ for both) while those with current psychiatric disorders had reduced blood flow only in the left middle cerebral artery territory ($P < 0.05$). These data indicate that patients with CFS have reduced absolute cortical blood flow in rather broad areas when compared with data from healthy controls and that those devoid of psychopathology had the most reductions in cortical flow. These data support, in part, our earlier findings that patients devoid of psychopathology are the group most at risk of having some of the symptoms of CFS due to brain dysfunction. © 2006 Blackwell Publishing Ltd.

Smith W.R., Noonan C., Buchwald D.
Mortality in a cohort of chronically fatigued patients

2006 Psychological Medicine 36 (9); 1301 – 1306

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33746917560&partnerID=40>

Department of Psychiatry, Department of Behavioral Sciences and Medicine, University of Washington, Seattle, WA, United States; Harborview Medical Center, 325 9th Avenue, Seattle, WA 98104, United States Background.

Comprehensive studies of mortality among patients with chronic fatigue (CF) and chronic fatigue syndrome (CFS) have not been published, but several sources suggest that CFS is associated with an elevated risk for suicide. Method. Data on 1201 chronically fatigued patients followed in a university-affiliated tertiary-care clinic for up to 14 years were submitted to the Center for Disease Control and Prevention (CDC) National Death Index (NDI) to evaluate all-cause and suicide-caused death rates against standardized mortality rates (SMRs). We used Life Table Analysis to examine the influence of sex and diagnoses of CFS and depression. Results. All-cause mortality in chronically fatigued patients was no higher than expected, but suicide-caused death rates were more than eight times higher than in the US general population. The significant elevation in the SMR of suicide was restricted to those who did not meet criteria for CFS [SMRCF=14.2, 95% confidence interval (CI) 5.7-29.3 versus SMRCFS=3.6, 95% CI 0.4-12.9]. Among chronically fatigued patients who did not meet CFS criteria, those with a lifetime history of major depression (MD) had higher suicide-caused death rates than among their non-depressed counterparts (SMRMD=19.1, 95% CI 7.0-41.5 versus SMRNMD=5.6, 95% CI 0.1-31.4), although the difference was not significant. Conclusions. CFS does not appear to be associated with increased all-cause mortality or suicide rates. Clinicians, however, should carefully evaluate patients with CF for depression and suicidality. © 2006 Cambridge University Press.

Michielsen H.J., Van Houdenhove B., Leirs I., Vandebroek A., Onghena P.
Depression, attribution style and self-esteem in chronic fatigue syndrome and fibromyalgia patients: Is there a link?

2006 Clinical Rheumatology 25 (2); 183 – 188

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33644866384&partnerID=40>

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The aims of the present study were to compare a single diagnosis (chronic fatigue syndrome, CFS) and a double diagnosis (CFS + fibromyalgia, CFS + FM) group regarding depression, attribution style and self-esteem as well as to examine whether attribution style is a mediator in the relationship between self-esteem and depression. Eighty-five patients (CFS: 47, CFS + FM: 38) completed questionnaires on attribution style, self-esteem and depression. The single and double diagnosis groups tended to differ slightly, but the differences were never statistically significant. In addition, only one condition was met of the four conditions mentioned by Baron and Kenny to establish that mediation exists between two variables. In conclusion, an external attribution style does not protect the CFS or CFS + FM patients with a low self-esteem from depression. The prevalence rate of depression was high in both patient samples, of which clinicians should be aware. © Clinical Rheumatology 2005.

Luyten P., Van Houdenhove B., Cosyns N., Van den Broeck A.-L.

Are patients with chronic fatigue syndrome perfectionistic - Or were they? A case-control study

2006 Personality and Individual Differences 40 (7); 1473 – 1483

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This study investigated the relationship between premorbid and postmorbid perfectionism, fatigue, and severity of depression in 43 CFS patients and 80 university students. Perfectionism in CFS patients and students was measured by the Multidimensional Perfectionism Scale (MPS-F; Frost, R. O., Marten, P., Lahart, C. M., & Rosenblate, R., 1990). CFS patients also retrospectively reported premorbid levels of perfectionism using a modified MPS-F. Results showed that CFS patients reported higher premorbid and postmorbid levels of both adaptive and maladaptive perfectionism compared to normal controls, although CFS attenuated certain aspects of perfectionism. Perfectionism was associated with severity of depression in CFS patients, even after controlling for demographic variables and concurrent levels of fatigue. Perfectionism was also associated with severity of fatigue in students, but not in CFS patients. Overall, results suggest that there may be no simple dichotomous distinction between adaptive and maladaptive perfectionism. Theoretical and clinical implications of these findings are discussed. © 2006 Elsevier Ltd. All rights reserved.

Kato K., Sullivan P.F., Evengard B., Pedersen N.L.

Premorbid predictors of chronic fatigue

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33750744410&partnerID=40>

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Context: Chronic fatigue syndrome is a disabling problem characterized by persistent fatigue lasting at least 6 months with a number of ancillary symptoms. Although the etiology of chronic fatiguing illness is unknown, some evidence suggests that stress may confer increased risk for development of the disorder. Moreover, subjects with chronic fatiguing illness may have distinctive personality traits, although this finding could reflect confounding by other mechanisms. Objective: To assess the prospective association of premorbid self-reported stress and personality with chronic fatigue-like illness. Design: Prospective nested case-control study in a population-based sample. Setting: General community. Participants: From the Swedish Twin Registry, 19 192 twins born between January 1, 1935, and December 31, 1958. Main Outcome Measures: Information about current chronic fatiguing illnesses was obtained from computer-assisted telephone interviews conducted between 1998 and 2002. Self-reported stress (based on a single question) and personality scales (emotional instability and extraversion in the Eysenck Personality Inventory) were measured from 1972 to 1973 by a mailed questionnaire. Relative risks were estimated with case-control analyses (matched for age and sex) and co-twin control analyses (comparing discordant pairs). Results: Higher emotional instability and self-reported stress in the premorbid period were associated with higher risk for chronic fatigue-like illness in matched case-control analyses (odds ratios, 1.72 and 1.64, respectively). In co-twin control analyses, relative risk of emotional instability decreased to 1.02 whereas that of stress increased considerably to 5.81. There was no association between extraversion and fatigue. Conclusions: Elevated premorbid stress is a significant risk factor for chronic fatigue-like illness, the effect of which may be buffered by genetic influences. Emotional instability assessed 25 years earlier is associated with chronic fatigue through genetic mechanisms contributing to both personality style and expression of the disorder. These findings suggest

plausible mechanisms for chronic fatiguing illness. ©2006 American Medical Association. All rights reserved.

Capuron L., Welberg L., Heim C., Wagner D., Solomon L., Papanicolaou D.A., Craddock R.C., Miller A.H., Reeves W.C.

Cognitive dysfunction relates to subjective report of mental fatigue in patients with chronic fatigue syndrome

2006 *Neuropsychopharmacology* 31 (8); 1777 – 1784

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Patients with chronic fatigue syndrome (CFS) frequently complain of cognitive dysfunction. However, evidence of cognitive impairment in CFS patients has been found in some, but not other, studies. This heterogeneity in findings may stem from the relative presence of mental fatigue in the patient populations examined. The present study assessed this possibility in a population-based sample of CFS patients. In all, 43 patients with CFS defined by the criteria of the 1994 research case definition using measurements recommended by the 2003 International CFS Study Group, and 53 age-, sex-, and race/ethnicity-matched nonfatigued subjects were included in the study. Mental fatigue was assessed using the mental fatigue subscale of the multidimensional fatigue inventory. Cognitive function was evaluated using an automated battery of computerized tests (Cambridge neuropsychological test automated battery (CANTAB)) that assessed psychomotor function, planning and problem-solving abilities, and memory and attentional performance. CFS patients with significant complaints of mental fatigue (score of mental fatigue 2 standard deviations above the mean of nonfatigued subjects) exhibited significant impairment in the spatial working memory and sustained attention (rapid visual information processing) tasks when compared to CFS patients with low complaints of mental fatigue and nonfatigued subjects. In CFS patients with significant mental fatigue, sustained attention performance was impaired only in the final stages of the test, indicating greater cognitive fatigability in these patients. CFS patients with low mental fatigue displayed performance comparable to nonfatigued subjects on all tests of the CANTAB battery. These findings show strong concordance between subjective complaints of mental fatigue and objective measurement of cognitive impairment in CFS patients and suggest that mental fatigue is an important component of CFS-related cognitive dysfunction. © 2006 Nature Publishing Group All rights reserved.

Wallman K.E., Morton A.R., Goodman C., Grove R.

Reliability of physiological, psychological, and cognitive variables in chronic fatigue syndrome

2005 *Research in Sports Medicine* 13 (3); 231 – 241

<http://www.scopus.com/inward/record.url?eid=2-s2.0-27344460772&partnerID=40>

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The purpose of this study was to assess the reliability of specific physiological, psychological, and cognitive variables in 31 chronic fatigue syndrome (CFS) subjects and 31 matched control subjects. All variables were assessed weekly over a 4-week period and reliability was determined using an intraclass correlation coefficient (ICC). Results ranged from moderately to highly reliable for all

variables assessed, except for mental and physical fatigue, which were of questionable reliability in both groups (ICC = 0.61 and 0.65, respectively, for the CFS group; 0.62 and 0.52 for the control group). A Pearson product-moment correlation analysis that compared exercise performance with all psychological variables assessed, demonstrated a significant relationship between exercise performance and depression ($r = .41$, $P = .02$) in week 3 only, suggesting minimal association between objective performance and psychological responses. These correlation results support a central, as opposed to a peripheral, basis to the sensation of fatigue in CFS. Copyright © Taylor & Francis Inc.

Richards J., Turk J., White S.

Children and adolescents with Chronic Fatigue Syndrome in non-specialist settings: Beliefs, functional impairment and psychiatric disturbance

2005 European Child and Adolescent Psychiatry 14 (6); 310 – 318

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Background: Adolescents with Chronic Fatigue Syndrome (CFS) seen in specialist centres have substantial psychological and functional impairment. Beliefs about activity levels may be important in the development of CFS. Method: The aim was to investigate psychological and functional impairment, and beliefs in children and adolescents with CFS recruited from non-specialist services. A total of 30 such individuals participated, and 30 young people with Inflammatory Bowel Disease (IBD) formed the comparison group. Results: Emotional symptoms and disorder were high in both groups. In all, 50% of those with CFS and 30% with IBD reached the threshold for emotional disorder according to the Strengths and Difficulties Questionnaire (SDQ) parent report, although this difference did not reach statistical significance. Participants with CFS scored statistically significantly higher on measures of functional impairment, including school non-attendance, compared to those with IBD. According to questionnaire responses, those with CFS were statistically significantly more likely to favour rest rather than exercise compared to those with IBD. Comparison of parental beliefs did not show such a difference. Conclusions: These young people with CFS were at high risk of psychiatric disorder. They were substantially disabled when compared to individuals with a known chronic illness. Also, as a group, they were characterised by a preference for rest rather than exercise. © Steinkopff Verlag 2005.

Prins J., Bleijenberg G., Rouweler E.K., Van Der Meer J.

Effect of psychiatric disorders on outcome of cognitive-behavioural therapy for chronic fatigue syndrome

2005 British Journal of Psychiatry 187 (AUG.); 184 – 185

<http://www.scopus.com/inward/record.url?eid=2-s2.0-23744511362&partnerID=40>

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Psychiatric disorders have been associated with poor outcome in individuals with chronic fatigue syndrome (CFS). This study examines the impact of psychiatric disorders on outcome of cognitive-behavioural therapy (CBT). Psychiatric diagnoses were assessed with a structured psychiatric

interview in a CBT trial of 270 people with CFS. Lifetime and current psychiatric disorders were found in 50 and 32% respectively. No significant differences in fatigue severity and functional impairment following treatment were found between participants with and without psychiatric diagnoses.

Henderson M., Tannock C.

Use of depression rating scales in chronic fatigue syndrome

2005 Journal of Psychosomatic Research 59 (3); 181 – 184

<http://www.scopus.com/inward/record.url?eid=2-s2.0-25644436222&partnerID=40>

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Objective: The aim of this study was to examine the performance of three commonly used depression rating scales in a hospital sample of patients with chronic fatigue syndrome (CFS). **Methods:** Sixty-one patients with CDC criteria for CFS completed the General Health Questionnaire (GHQ), the Hamilton Depression Scale (HAM-D) and the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D). Current psychiatric status was assessed using the Structured Clinical Interview for DSM-III-R. Disorders: Patient version (SCID-P). Receiver operating curves were drawn for each of the depression rating scales. **Results:** Thirty-one percent of the patients were depressed according to the SCID-P. Using the standard cut-offs, both GHQ and HAM-D overestimated the number of depressed patients, whilst the HADS-D underestimated the number. The receiver operating curves suggest that the optimum cut-offs for GHQ, HAM-D and HADS-D in this population are 7/8, 13/14 and 8/9, respectively. **Conclusions:** Standard cutoffs may not be appropriate when using depression rating scales in CFS patients in a tertiary care setting. © 2005 Elsevier Inc. All rights reserved.

Gallagher A.M., Coldrick A.R., Hedge B., Weir W.R.C., White P.D.

Is the chronic fatigue syndrome an exercise phobia? A case control study

2005 Journal of Psychosomatic Research 58 (4); 367 – 373

<http://www.scopus.com/inward/record.url?eid=2-s2.0-21344472339&partnerID=40>

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Objective: The aim of this study was to test whether patients with chronic fatigue syndrome (CFS) have an exercise phobia, by measuring anxiety-related physiological and psychological reactions to ordinary activity and exercise. **Methods:** Patients and healthy but sedentary controls were assessed over 8 h of an ordinary day, and before, during and after an incremental exercise test on a motorised treadmill. To avoid confounding effects, those with a comorbid psychiatric disorder were excluded. Heart rate, galvanic skin resistance (GSR) and the amount of activity undertaken were measured, along with state and trait measures of anxiety. **Results:** Patients with CFS were more fatigued and sleep disturbed than were the controls and noted greater effort during the exercise test. No statistically significant differences were found in either heart rate or GSR both during a normal day and before, during and after the exercise test. Patients with CFS were more symptomatically anxious at all times, but this did not increase with exercise. **Conclusion:** The data suggest that CFS patients without a comorbid psychiatric disorder do not have an exercise phobia. © 2005 Elsevier Inc. All rights reserved.

De Lange F.P., Kalkman J.S., Bleijenberg G., Hagoort P., Van Der Meer J.W.M., Toni I.
Gray matter volume reduction in the chronic fatigue syndrome

2005 NeuroImage 26 (3); 777 - 781

<http://www.scopus.com/inward/record.url?eid=2-s2.0-20444505710&partnerID=40>

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The chronic fatigue syndrome (CFS) is a disabling disorder of unknown etiology. The symptomatology of CFS (central fatigue, impaired concentration, attention and memory) suggests that this disorder could be related to alterations at the level of the central nervous system. In this study, we have used an automated and unbiased morphometric technique to test whether CFS patients display structural cerebral abnormalities. We mapped structural cerebral morphology and volume in two cohorts of CFS patients (in total 28 patients) and healthy controls (in total 28 controls) from high-resolution structural magnetic resonance images, using voxel-based morphometry. Additionally, we recorded physical activity levels to explore the relation between severity of CFS symptoms and cerebral abnormalities. We observed significant reductions in global gray matter volume in both cohorts of CFS patients, as compared to matched control participants. Moreover, the decline in gray matter volume was linked to the reduction in physical activity, a core aspect of CFS. These findings suggest that the central nervous system plays a key role in the pathophysiology of CFS and point to a new objective and quantitative tool for clinical diagnosis of this disabling disorder. © 2005 Elsevier Inc. All rights reserved.

Cook D.B., Nagelkirk P.R., Peckerman A., Poluri A., Mores J., Natelson B.H.
Exercise and cognitive performance in chronic fatigue syndrome

2005 Medicine and Science in Sports and Exercise 37 (9); 1460 – 1467

<http://www.scopus.com/inward/record.url?eid=2-s2.0-25444524051&partnerID=40>

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Purpose: To determine the effect of submaximal steady-state exercise on cognitive performance in patients with chronic fatigue syndrome (CFS) alone, CFS with comorbid fibromyalgia FM (CFS+FM), and sedentary healthy controls (CON). Methods: Twenty CFS-only patients, 19 CFS+FM, and 26 CON completed a battery of cognitive tests designed to assess speed of information processing, variability, and efficiency. Tests were performed at baseline, immediately before, and twice following 25 min of either cycle ergometry set at 40% of peak oxygen capacity or quiet rest. Results: There were no group differences in average percentage of peak oxygen consumption during exercise (CFS = 45%; CFS+FM = 47%; Control = 43%; $P = 0.2$). There were no significant effects of acute exercise on cognitive performance for any group. At baseline, one-way ANOVA indicated that CFS patients displayed deficits in speed of processing, performance variability, and task efficiency during several cognitive tests compared with healthy controls. However, the CFS+FM patients were not different than controls. Repeated measures ANOVA indicated that across all tests (pre- and postexercise) CFS, but not CFS+FM, were significantly less consistent ($F_{2,59} = 3.7, P = 0.03$) and less efficient ($F_{2,59} = 4.6, P = 0.01$) than controls. Conclusion: CFS patients without comorbid FM exhibit subtle cognitive deficits in terms of speed, consistency, and efficiency that are not improved or exacerbated by light exercise. Importantly, our data suggest that CFS+FM patients do not exhibit cognitive deficits either pre- or postexercise. These results highlight the importance of disease

heterogeneity in studies determining acute exercise and cognitive function in CFS. Copyright © 2005 by the American College of Sports Medicine.

Van Hoof E., De Meirleir K.

The influence of chronic fatigue syndrome on the personality profile: A case report

2004 Journal of Chronic Fatigue Syndrome 12 (3); 63 – 71

<http://www.scopus.com/inward/record.url?eid=2-s2.0-28844436927&partnerID=40>

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Objective: Chronic fatigue syndrome (CFS) functionally impairs many patients. Despite numerous studies and reviews in CFS, little is known about the behavioral consequences. Several researchers have already suggested the influential role of personality as a possible predisposing or perpetuating factor. Method: A case study is presented of a 34-year-old man with a history of CFS. Psychological profiling using the MMPI-2 was performed during the course of his condition. Results: His passive-aggressive manner during the medical encounter was underscored by his personality profile (code type 3-2). After his recovery, however, a spike 3 profile emerged indicating a fulfilled individual. Somatic items included in the inventory, created a secondary increase of the clinical scales. Physical complaints diminished as his condition improved and subsequently, decreased the clinical scales. Conclusion: The relevance of classifying personality characteristics in CFS patients as traits could not be supported by this case report. © 2004 by The Haworth Press, Inc. All rights reserved.

Skapinakis P., Lewis G., Mavreas V.

Temporal relations between unexplained fatigue and depression: Longitudinal data from an international study in primary care

2004 Psychosomatic Medicine 66 (3); 330 - 335

<http://www.scopus.com/inward/record.url?eid=2-s2.0-2442682857&partnerID=40>

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Objective: Unexplained fatigue syndromes, such as chronic fatigue syndrome and neurasthenia, are strongly associated with depression, but the temporal nature of this association is not clear. Methods: The authors examined this issue by using data from the World Health Organization collaborative study of psychological problems in general health care. Three thousand two hundred one subjects from 15 primary care centers in 14 countries were followed up for 12 months. The Composite International Diagnostic Interview was the main instrument used. Odds ratios and their 95% confidence intervals (CI) were calculated using logistic regression models adjusted for sociodemographic variables, physical morbidity and intercenter variability. Results: Cases of depression were found to have an increased risk of developing a new episode of unexplained fatigue at follow-up with an adjusted odds ratio of 4.15 (95% CI = 2.64-6.54). Similarly, cases of unexplained fatigue were found to have an increased risk of developing a new episode of depression at follow-up with an adjusted odds ratio of 2.76 (95% CI = 1.32-5.78). Further adjustment for subthreshold symptoms at baseline weakened the reported associations, especially between fatigue and development of a new episode of depression, but these remained significant. Conclusions: The findings support the view that unexplained fatigue and depression might act as independent risk factors for each other.

Siemionow V., Fang Y., Calabrese L., Sahgal V., Yue G.H.

Altered central nervous system signal during motor performance in chronic fatigue syndrome

2004 Clinical Neurophysiology 115 (10); 2372 – 2381

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4444303522&partnerID=40>

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Objective: The purpose of this study was to determine whether brain activity of chronic fatigue syndrome (CFS) patients during voluntary motor actions differs from that of healthy individuals. **Methods:** Eight CFS patients and 8 age- and gender-matched healthy volunteers performed isometric handgrip contractions at 50% maximal voluntary contraction level. They first performed 50 contractions with a 10 s rest between adjacent trials - 'Non-Fatigue' (NFT) task. Subsequently, the same number of contractions was performed with only a 5 s rest between trials - 'Fatigue' (FT) task. Fifty-eight channels of surface EEG were recorded simultaneously from the scalp. Spectrum analysis was performed to estimate power of EEG frequency in different tasks. Motor activity-related cortical potential (MRCP) was derived by triggered averaging of EEG signals associated with the muscle contractions. **Results:** Major findings include: (i) Motor performance of the CFS patients was poorer than the controls. (ii) Relative power of EEG theta frequency band (4-8 Hz) during performing the NFT and FT tasks was significantly greater in the CFS than control group ($P < 0.05$). (iii) The amplitude of MRCP negative potential (NP) for the combined NFT and FT tasks was higher in the CFS than control group ($P < 0.05$). (iv) Within the CFS group, the NP was greater for the FT than NFT task ($P < 0.01$), whereas no such difference between the two tasks was found in the control group. **Conclusions:** These results clearly show that CFS involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue. **Significance:** Physical activity-induced EEG signal changes may serve as physiological markers for more objective diagnosis of CFS. © 2004 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.

Pazderka-Robinson H., Morrison J.W., Flor-Henry P.

Electrodermal dissociation of chronic fatigue and depression: Evidence for distinct physiological mechanisms

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-3042828269&partnerID=40>

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Chronic fatigue syndrome (CFS) has an estimated prevalence between 0.5% and 3%, yet its diagnosis remains contentious. CFS is characterized by subjective symptoms that can be difficult to verify; moreover, depression is a commonly reported CFS complaint, whereas fatigue is a common symptom of depression. Our primary goal was dissociation of these disorders using psychophysiological methods. As previous research has implicated the autonomic nervous system in CFS, we conducted what we believe to be the first analysis of bilateral electrodermal and skin temperature responses of dextral females in a cross-modal orienting task, to investigate differences between these two patient groups and controls. A multivariate analysis of variance (MANOVA) examining three measures of electrodermal activity revealed prestimulus tonic skin conductance levels (SCLs) were markedly lower for the CFS group, with no difference between controls and depressives. Concurrent skin temperature levels were higher for the CFS group than the other two groups. These findings indicate that, despite overtly similar cognitive and symptom profiles,

depression and CFS patients can be differentiated with psychophysiological measures. This study adds to the growing body of evidence demonstrating that CFS and depression have distinct neurobiological profiles, consistent with unique aetiologies. © 2004 Elsevier B.V. All rights reserved.

Okada T., Tanaka M., Kuratsune H., Watanabe Y., Sadato N.

Mechanisms underlying fatigue: A voxel-based morphometric study of chronic fatigue syndrome

2004 BMC Neurology 4

<http://www.scopus.com/inward/record.url?eid=2-s2.0-12944316322&partnerID=40>

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Background: Fatigue is a crucial sensation that triggers rest, yet its underlying neuronal mechanisms remain unclear. Intense long-term fatigue is a symptom of chronic fatigue syndrome, which is used as a model to study the mechanisms underlying fatigue. Methods: Using magnetic resonance imaging, we conducted voxel-based morphometry of 16 patients and 49 age-matched healthy control subjects. Results: We found that patients with chronic fatigue syndrome had reduced gray-matter volume in the bilateral prefrontal cortex. Within these areas, the volume reduction in the right prefrontal cortex paralleled the severity of the fatigue of the subjects. Conclusion: These results are consistent with previous reports of an abnormal distribution of acetyl-L-carnitine uptake, which is one of the biochemical markers of chronic fatigue syndrome, in the prefrontal cortex. Thus, the prefrontal cortex might be an important element of the neural system that regulates sensations of fatigue. © 2004 Okada et al; licensee BioMed Central Ltd.

Nijs J., De Meirleir K., Duquet W.

Kinesiophobia in chronic fatigue syndrome: Assessment and associations with disability

2004 Archives of Physical Medicine and Rehabilitation 85 (10); 1586 – 1592

<http://www.scopus.com/inward/record.url?eid=2-s2.0-5344221560&partnerID=40>

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Objectives To investigate aspects of the validity of the total scores of the Tampa Scale for Kinesiophobia (TSK), Dutch Version, which was modified to make it an appropriate questionnaire for the assessment of kinesiophobia (fear of movement) in chronic fatigue syndrome (CFS) patients (the Dutch TSK-CFS), and, using this assessment tool, to examine the associations between kinesiophobia, exercise capacity, and activity limitations and participation restrictions in patients with CFS. Design Prospective observational studies. Setting An outpatient fatigue clinic. Participants In the first study, 40 patients fulfilling the 1994 US Centers for Disease Control and Prevention (CDC) criteria for CFS were enrolled. The sample of the second study consisted of 51 CDC-defined patients with CSF. Interventions Not applicable. Main outcome measures Study 1: Subjects completed a set of questionnaires; the Utrechtse Coping List (UCL), the Dutch TSK-CFS, and the Dutch Baecke Questionnaire of Habitual Physical Activity. Study 2: All patients completed 2 questionnaires (Chronic Fatigue Syndrome Activities and Participation Questionnaire [CFS-APQ], Dutch TSK-CFS) and performed a maximal exercise stress test on a bicycle ergometer. The heart rate was monitored continuously by use of an electrocardiograph. Metabolic and ventilatory parameters were measured through spirometry. Results Study 1: The Cronbach $\hat{\pm}$ coefficient for the individual item scores on the TSK-CFS was .80. The total scores on the Dutch TSK-CFS showed a

statistically significant correlation with both the avoidance/abide subscale of the UCL (Spearman $\rho = .35$, $P = .029$) and the total score of the Baecke Questionnaire ($\rho = -.45$, $P = .004$). Study 2: The total scores on the Dutch TSK-CFS showed a statistically significant correlation with the total scores on the CFS-APQ ($\rho = .39$, $P = .004$). No statistically significant associations were observed between the exercise capacity parameters and the total scores on the Dutch TSK-CFS. Conclusions These results provide evidence for the internal consistency and the convergent and congruent validity of the scores obtained by use of the Dutch TSK-CFS. Kinesiophobia appears to be associated with activity limitations/participation restrictions but not with exercise capacity in patients with CFS. © 2004 by the American Congress of Rehabilitation Medicine and the American Academy of Physical Medicine and Rehabilitation.

Miike T., Tomoda A., Jhodoi T., Iwatani N., Mabe H.
Learning and memorization impairment in childhood chronic fatigue syndrome manifesting as school phobia in Japan

2004 Brain and Development 26 (7); 442 - 447

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4444305028&partnerID=40>

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For the last 15 years, we have tried to understand the pathophysiology of childhood chronic fatigue syndrome (CCFS) in Japan. In this condition, two major symptoms are important: easy fatigability and disturbed learning and memorization. In CCFS patients we clinically evaluated autonomic nervous system function, circadian rhythm of hormonal secretion (melatonin, cortisol and 3-endorphin), core body temperature, and sleep-wake pattern. Most patients showed autonomic nervous system dysfunction and circadian rhythm disturbances, similar to those observed in jet lag. Radiological imaging studies (SPECT, Xe-CT, and MRS) revealed decreased blood flow in the frontal and thalamic areas, and accumulation of choline in the frontal lobe. We analyzed the relationship between the laboratory data and clinical symptoms in CCFS. © 2004 Elsevier B.V. All rights reserved.

Mahurin R.K., Goldberg J.H., Claypoole K.H., Arguelles L., Ashton S., Buchwald D.
Cognitive Processing in Monozygotic Twins Discordant for Chronic Fatigue Syndrome

2004 Neuropsychology 18 (2); 232 - 239

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1942438158&partnerID=40>

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Twenty-one pairs of monozygotic twins discordant for chronic fatigue syndrome (CFS) and 21 matched healthy control (HC) subjects were assessed with 5 untimed tests and 5 timed tests from the computer-based NeuroCognitive Assessment Battery (R. K. Mahurin, 1993). Random effects regression showed no difference between CFS and healthy twins on any of the cognitive tests. Further, the twin groups did not differ from the HC group on any content-dependent measure. In contrast, both sets of twins performed worse than the HC group on all speed-dependent tests except Finger Tapping. Self-rated fatigue and dysphoric mood were only weakly correlated with cognitive performance. These data point toward a shared genetic trait related to information processing that is manifest in the CFS context. The findings have implications for differentiating genetic and acquired vulnerability in the symptomatic expression of the disorder.

Henderson M., Tannock C.

Objective assessment of personality disorder in chronic fatigue syndrome

2004 Journal of Psychosomatic Research 56 (2); 251 – 254

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1542328121&partnerID=40>

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Objectives This study aims to objectively assess the prevalence and nature of personality disorders in depressed and nondepressed chronic fatigue syndrome (CFS) patients and compare this to depressed and healthy control groups. **Methods** Sixty-one patients attending a tertiary referral clinic with chronic fatigue syndrome, 40 psychiatric inpatients with depressive disorder and 45 healthy medical students completed the Structured Clinical Interview for DSM-III-R Diagnoses (SCID-II) in addition to providing routine clinical and demographic information. **Results** Thirty-nine percent of the CFS group, 73% of the depressed group and 4% of the healthy group were diagnosed with personality disorders. Cluster C disorders were the most common in both the CFS and depressed group. The depressed CFS patients had more Cluster B personality disorders than nondepressed CFS patients. Overall for CFS patients there was no association between mood state and personality disorder. **Conclusions** High levels of personality disorder are found on objective assessment of CFS patients attending a teaching hospital clinic. This cannot be accounted for by comorbid depression. © 2004 Elsevier Inc. All rights reserved.

DeLuca J., Christodoulou C., Diamond B.J., Rosenstein E.D., Kramer N., Ricker J.H., Natelson B.H.
The Nature of Memory Impairment in Chronic Fatigue Syndrome

2004 Rehabilitation Psychology 49 (1); 62 - 70

<http://www.scopus.com/inward/record.url?eid=2-s2.0-0842349465&partnerID=40>

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Objective: Examine whether memory impairment in chronic fatigue syndrome (CFS) is due to deficits in acquisition, storage, or retrieval. **Study Design:** Prospective, between-groups design. **Participants:** Twenty-nine CFS participants without psychiatric comorbidity (CFS-noPsych) and 22 participants with an Axis I psychiatric diagnosis since CFS onset. Two control groups: 30 healthy persons and 19 participants with rheumatoid arthritis. **Main Outcome Measures:** After being equated for initial learning, recall and recognition were assessed after 30- and 90-min delays. **Results:** Both CFS groups required more trials to learn the word list than did healthy controls. The CFS-noPsych group performed significantly below healthy controls on recall but not on recognition. Learning/acquisition correlated with measures of complex information processing and not with depressive symptomatology or fatigue. **Conclusions:** Impaired verbal learning and memory in CFS is primarily a result of deficient acquisition.

Deluca J., Christodoulou C., Diamond B.J., Rosenstein E.D., Kramer N., Natelson B.H.
Working memory deficits in chronic fatigue syndrome: Differentiating between speed and accuracy of information processing

2004 Journal of the International Neuropsychological Society 10 (1); 101 – 109
<http://www.scopus.com/inward/record.url?eid=2-s2.0-1642523391&partnerID=40>

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To examine the relative influence of speed of information processing versus working memory ability, CFS participants with psychiatric comorbidity (CFS-Psych) and CFS without a psychiatric history (CFS-noPsych) were examined on tests of visual and auditory processing speed and visual and auditory working memory. Compared to healthy controls (HC) and a group of participants with rheumatoid arthritis (RA), the CFS-noPsych group displayed significantly reduced performance on tests of information processing speed, but not on tests of working memory. No significant differences were observed between the CFS-Psych group and any other group in the study. The implications of group heterogeneity on the understanding of cognitive impairment in CFS are discussed.

De Lange F.P., Kalkman J.S., Bleijenberg G., Hagoort P., Werf S.P.Vd., Van Der Meer J.W.M., Toni I.
Neural correlates of the chronic fatigue syndrome - An fMRI study

2004 Brain 127 (9); 1948 - 1957
<http://www.scopus.com/inward/record.url?eid=2-s2.0-4344669823&partnerID=40>

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Chronic fatigue syndrome (CFS) is characterized by a debilitating fatigue of unknown aetiology. Patients who suffer from CFS report a variety of physical complaints as well as neuropsychological complaints. Therefore, it is conceivable that the CNS plays a role in the pathophysiology of CFS. The purpose of this study was to investigate neural correlates of CFS, and specifically whether there exists a linkage between disturbances in the motor system and CFS. We measured behavioural performance and cerebral activity using rapid event-related functional MRI in 16 CFS patients and 16 matched healthy controls while they were engaged in a motor imagery task and a control visual imagery task. CFS patients were considerably slower on performance of both tasks, but the increase in reaction time with increasing task load was similar between the groups. Both groups used largely overlapping neural resources. However, during the motor imagery task, CFS patients evoked stronger responses in visually related structures. Furthermore, there was a marked between-groups difference during erroneous performance. In both groups, dorsal anterior cingulate cortex was specifically activated during error trials. Conversely, ventral anterior cingulate cortex was active when healthy controls made an error, but remained inactive when CFS patients made an error. Our results support the notion that CFS may be associated with dysfunctional motor planning. Furthermore, the between-groups differences observed during erroneous performance point to motivational disturbances as a crucial component of CFS.

Brimacombe M., Lange G., Bisuchio K., Ciccone D.S., Natelson B.
Cognitive function index for patients with chronic fatigue syndrome

2004 Journal of Chronic Fatigue Syndrome 12 (4); 3 – 23

<http://www.scopus.com/inward/record.url?eid=2-s2.0-30044434921&partnerID=40>

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Background: A comprehensive approach to assessing neuropsychological deficits in CFS patients is developed by assessing cognitive function across a number of domains using a battery of tests, rather than relying on any single instrument. **Objective:** A factor analytic approach was employed to examine the underlying dimensionality of 15 standard cognitive function related test variables in CFS patients. A cognitive function index (CFI) was then developed using appropriately weighted and interpreted factors. **Methods:** Factor analysis was applied to an initial sample of 65 CFS patients, identifying eight factors accounting for over 70% of total variation. This factor structure was then independently verified on a separate sample of 124 CFS patients. An overall combined CFS sample of 212 was then used to derive the CFI using an appropriately interpreted and weighted average of the derived factors. **Results:** After including age and education as separate factors, the CFI consists of nine factors accounting for 70% of total variation in the overall CFS group. The CFI was not affected by the presence of current psychiatric comorbidity. A cut-off score for cognitive dysfunction was established using the lower quartile value of a group of sedentary controls on the same index. **Conclusions:** The CFI will provide a useful summary measure for researchers investigating cognitive function performance in CFS patients. It does not replace existing individual specialized tests. © 2004 by The Haworth Press, Inc. All rights reserved.

Axe E.K., Satz P., Rasgon N.L., Fawzy F.I.

Major depressive disorder in chronic fatigue syndrome: A CDC surveillance study

2004 Journal of Chronic Fatigue Syndrome 12 (3); 7 – 23

<http://www.scopus.com/inward/record.url?eid=2-s2.0-28844486809&partnerID=40>

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Background: Controversy continues to exist as to whether Chronic Fatigue Syndrome is a psychological/psychiatric disorder. To further understand this condition the Centers for Disease Control (CDC) conducted a Surveillance Study. The CDC partitioned 565 subjects with fatiguing illnesses into four diagnostic groups, one of which met the 1988 CDC criteria for CFS. The non-CFS groups had either insufficient severity (idiopathic), medical exclusions or prior psychiatric disorders. **Objectives:** The present study reports on the psychiatric features in that study, estimates the time of onset of Major Depressive Disorder (MDD) and looks for possible relationships between 1988 CDC criteria for Chronic Fatigue Syndrome and psychiatric disorders. **Methods:** The study design is cross-sectional. The Diagnostic Interview Schedule (DIS) assessed for four Axis I psychiatric disorders. Time of onset of MDD was estimated from the DIS and validated by an examination of the medical records. Odds ratios and confidence intervals were calculated as tests of association between 1988 CDC criteria and psychiatric disorders. **Results:** Subjects classified as CFS and non-CFS had similar rates of psychiatric disorders. A minority of subjects had preexisting MDD. Three 1988 CDC criteria were associated with current MDD whilst no criteria were associated with prior MDD. **Conclusions:** CFS subjects did not demonstrate any unique patterns of psychiatric disorders. MDD may not be an

important predisposing factor for CFS or the other fatiguing illnesses. Some 1988 CDC criteria may be preferentially endorsed by subjects with current MDD. Å© 2004 by The Haworth Press, Inc. All rights reserved.

Andersen M.M., Permin H., Albrecht F.

Illness and disability in Danish Chronic Fatigue Syndrome patients at diagnosis and 5-year follow-up

2004 Journal of Psychosomatic Research 56 (2); 217 – 229

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1542298140&partnerID=40>

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Objective: Evaluation of the life impact of Chronic Fatigue Syndrome (CFS) over 5 years. Methods: Thirty-three adult patients meeting 1988 and 1994 CDC case criteria answered identical questionnaires at diagnosis and 5 years later, when a retrospective questionnaire was also completed. Results: Work disability was very high and increased further, social isolation remained high, emotional adjustment improved. There were increased problems with reading and with allergies. Two measures of improvement were used: The relation between these measures was weak. Length of illness, extent of disability and emotional adjustment were poorly related to measures of improvement. Average illness scores were unchanged, but most individuals improved in some ways while worsening or remaining the same in others. Only one participant (3%) neared recovery, one other was substantially better but still severely disabled. Conclusion: CFS patients exhibit severe, long-term functional impairment. Substantial improvement is uncommon, less than 6%. Allergies and aspects of cognition may worsen, emotional adjustment often improves. Å© 2004 Elsevier Inc. All rights reserved.

Pain

Nijs J., Van De Putte K., Louckx F., Truijen S., De Meirleir K.

Exercise performance and chronic pain in chronic fatigue syndrome: The role of pain catastrophizing

2008 Pain Medicine 9 (8); 1164 - 1172

<http://www.scopus.com/inward/record.url?eid=2-s2.0-42649140689&partnerID=40>

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Objectives. This study aimed to examine the associations between bodily pain, pain catastrophizing, depression, activity limitations/ participation restrictions, employment status, and exercise performance in female patients with chronic fatigue syndrome (CFS) who experience widespread pain. **Design.** Cross-sectional observational study. **Setting.** A university-based clinic. **Patients.** Thirty-six female CFS patients who experienced widespread pain. **Outcome Measures.** Patients filled in the Medical Outcomes Short-Form 36 Health Status Survey, the Chronic Fatigue Syndrome Activities and Participation Questionnaire, the Beck Depression Inventory, and the Pain Catastrophizing Scale, and underwent a maximal exercise stress test with continuous monitoring of electrocardiographic and ventilatory parameters. **Results.** Pain catastrophizing was related to bodily pain ($r = -0.70$), depression ($r = 0.55$), activity limitations/participation restrictions ($r = 0.68$), various aspects of quality of life (r varied between -0.51 and -0.64), and exercise capacity (r varied between -0.41 and -0.61). Based on hierarchical multiple regression analysis, pain catastrophizing accounted for 41% of the variance in bodily pain in female CFS patients who experience chronic widespread musculoskeletal pain. Among the three subscale scores of the Pain Catastrophizing Scale, helplessness and rumination rather than magnification were strongly related to bodily pain. Neither pain catastrophizing nor depression was related to employment status. **Conclusions.** These data provide evidence favoring a significant association between pain catastrophizing, bodily pain, exercise performance, and self-reported disability in female patients with CFS who experience widespread pain. Further prospective longitudinal studying of these variables is required. © 2008 by American Academy of Pain Medicine.

Meeus M., Nijs J., Van de Wauwer N., Toeback L., Truijen S.

Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: An experimental study

2008 Pain 139 (2); 439 - 448

<http://www.scopus.com/inward/record.url?eid=2-s2.0-53049087260&partnerID=40>

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Deficient endogenous pain inhibition, e.g. Diffuse noxious inhibitory controls (DNIC), or hormonal abnormalities like hypocortisolism, could be responsible for chronic widespread pain in Chronic Fatigue Syndrome (CFS). Thirty-one CFS-patients with chronic pain and 31 healthy controls were subjected to spatial summation of thermal noxious stimuli by gradual immersion (ascending or descending) of the arm in warm water ($46 \text{ }^{\circ}\text{C}$). They rated pain intensity every 15 s. Every immersion took 2 min, alternated with 5 min rest. Before and after immersion, salivary cortisol was assessed. Overall pain ratings were higher in CFS-patients, but the evolution was not different between patients and controls, during both ascending and descending immersion. Pain intensity and immersed surface were only correlated during the descending session in both patients ($r = .334$) and controls ($r = .346$). When comparing the first and the last 15 s of every immersion, it was found that pain inhibition starts slower for CFS-patients in comparison to healthy subjects. Both pre- or post-values and cortisol response did

not differ between controls and patients. The drop in cortisol was significantly correlated to pain intensity in CFS (r between .357 and .402). In addition to the hyperalgesia in CFS, DNIC react slower to spatial summation of thermal noxious stimuli. We found no evidence for hypocortisolism in CFS, and the cortisol response to nociception was not different in CFS compared to healthy subjects. In conclusion, delayed pain inhibition may play a role in chronic widespread pain in CFS but further research is required. © 2008 International Association for the Study of Pain.

Geisser M.E., Donnell C.S., Petzke F., Gracely R.H., Clauw D.J., Williams D.A.
Comorbid somatic symptoms and functional status in patients with fibromyalgia and chronic fatigue syndrome: Sensory amplification as a common mechanism

2008 Psychosomatics 49 (3); 235 - 242

<http://www.scopus.com/inward/record.url?eid=2-s2.0-43649092953&partnerID=40>

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Background: Somatic symptoms are common in conditions such as fibromyalgia (FM) and chronic fatigue syndrome (CFS). Objective: Authors investigated a potential shared pathologic mechanism: a generalized perceptual abnormality where there is heightened responsiveness to varied sensory stimulation, including pain. Method: A composite measure of sensory sensitivity was created and compared with measures of somatic symptoms, comorbid psychological disturbances, and self-reported physical functioning in 38 patients with FM and/or CFS. Results: Sensory amplification influenced physical functioning indirectly through pain intensity, and physical symptoms and fatigue also independently contributed to physical functioning. Conclusion: Sensory amplification may be an underlying pathophysiologic mechanism in these disorders that is relatively independent of depression and depressive symptoms. © 2008 The Academy of Psychosomatic Medicine.

Ullrich P.M., Afari N., Jacobsen C., Goldberg J., Buchwald D.
Cold pressor pain sensitivity in monozygotic twins discordant for chronic fatigue syndrome

2007 Pain Medicine 8 (3); 216 - 222

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33947400146&partnerID=40>

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Objective. Individuals with chronic fatigue syndrome (CFS) experience many pain symptoms. The present study examined whether pain and fatigue ratings and pain threshold and tolerance levels for cold pain differed between twins with CFS and their cotwins without CFS. Design. Cotwin control design to assess cold pain sensitivity, pain, and fatigue in monozygotic twins discordant for CFS. Patients and Setting. Fifteen monozygotic twin pairs discordant for CFS recruited from the volunteer Chronic Fatigue Twin Registry at the University of Washington. Results. Although cold pain threshold and tolerance levels were slightly lower in twins with CFS than their cotwins without CFS, these differences failed to reach statistical significance. Subjective ratings of pain and fatigue at multiple time points during the experimental protocol among twins with CFS were significantly higher than ratings of pain ($P = 0.003$) and fatigue ($P < 0.001$) by their cotwins without CFS. Conclusions. These results, while preliminary, highlight the perceptual and cognitive components to the pain experience in CFS. Future studies should focus on examining the heritability of pain sensitivity and the underlying mechanisms involved in the perception of pain sensitivity in CFS. © American Academy of Pain Medicine.

Knoop H., Stulemeijer M., Prins J.B., van der Meer J.W.M., Bleijenberg G.
Is cognitive behaviour therapy for chronic fatigue syndrome also effective for pain symptoms?

2007 Behaviour Research and Therapy 45 (9); 2034 – 2043

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34547659127&partnerID=40>

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Patients with chronic fatigue syndrome (CFS) frequently report chronic pain symptoms. Cognitive behavioural therapy (CBT) for CFS results in a reduction of fatigue, but is not aimed at pain symptoms. In this study, we tested the hypothesis that a successful treatment of CFS can also lead to a reduction of pain. The second objective was to explore possible mechanisms of changes in pain. The third objective was to assess the predictive value of pain for treatment outcome. Data from two previous CBT studies were used, one of adult CFS patients (n=96) and one of adolescent CFS patients (n=32). Pain severity was assessed with a daily self-observation list at baseline and post-treatment. The location of pain in adults was assessed with the McGill Pain Questionnaire (MPQ). Patients were divided into recovered and non-recovered groups. Recovery was defined as reaching a post-treatment level of fatigue within normal range. Recovered adult and adolescent CFS patients reported a significant reduction of pain severity compared to non-recovered patients. Recovered adult patients also had fewer pain locations following treatment. The decrease in fatigue predicted the change in pain severity. In adult patients, a higher pain severity at baseline was associated with a negative treatment outcome. © 2007 Elsevier Ltd. All rights reserved.

Geisser M.E., Gracely R.H., Giesecke T., Petzke F.W., Williams D.A., Clauw D.J.
The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome

2007 European Journal of Pain 11 (2); 202 – 207

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33751416440&partnerID=40>

Chronic Pain and Fatigue Research Center, Department of Internal Medicine, Division of Rheumatology, Ann Arbor, MI, United States; Department of Physical Medicine and Rehabilitation, University of Michigan Health System, 325 E. Eisenhower Parkway, Ann Arbor, MI 48108, United States; Department of Anesthesiology and Intensive Care, University of Cologne, Cologne, Germany

Evoked or experimental pain is often used as a model for the study of clinical pain, yet there are little data regarding the relationship between the two. In addition, there are few data regarding the types of stimuli and stimulus intensities that are most closely related to clinical pain. In this study, 36 subjects with fibromyalgia (FM), chronic fatigue syndrome (CFS), or both syndromes were administered measures of clinical pain and underwent a dolorimetry evaluation. Subjects also underwent experimental pain testing utilizing heat and pressure stimulation. Stimulation levels evoking low, moderate and high sensory intensity, and comparable levels of unpleasantness, were determined for both types of stimuli using random staircase methods. Clinical pain was assessed using visual analogue ratings and the short form of the McGill Pain Questionnaire (MPQ). Ratings of heat pain sensation were not significantly associated with clinical pain ratings, with the exception of unpleasantness ratings at high stimulus intensities. Pain threshold and tolerance as assessed by dolorimetry were significantly associated with average measures of clinical pain. Both intensity and unpleasantness ratings of pressure delivered using random staircase methods were significantly associated with clinical pain at low, moderate and high levels, and the strength of the association was greater at increasingly noxious stimulus intensities. These findings suggest that random pressure stimulation as an experimental pain model in these populations more closely reflects the clinical pain for these conditions. These findings merit consideration when designing experimental studies of clinical pain associated with FM and CFS. © 2006 European Federation of Chapters of the International Association for the Study of Pain.

Nijs J., Meeus M., De Meirleir K.

Chronic musculoskeletal pain in chronic fatigue syndrome: Recent developments and therapeutic implications

2006 Manual Therapy 11 (3); 187 - 191

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33746531152&partnerID=40>

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Patients with chronic fatigue syndrome (CFS) experience chronic musculoskeletal pain which is even more debilitating than fatigue. Scientific research data gathered around the world enables clinicians to understand, at least in part, chronic musculoskeletal pain in CFS patients. Generalized joint hypermobility and benign joint hypermobility syndrome appear to be highly prevalent among CFS sufferers, but they do not seem to be of any clinical importance. On the other hand, pain catastrophizing accounts for a substantial portion of musculoskeletal pain and is a predictor of exercise performance in CFS patients. The evidence concerning pain catastrophizing is supportive of the indirect evidence of a dysfunctional pain processing system in CFS patients with musculoskeletal pain. CFS sufferers respond to incremental exercise with a lengthened and accentuated oxidative stress response, explaining muscle pain, postexertional malaise, and the decrease in pain threshold following graded exercise in CFS patients. Applying the scientific evidence to the manual physiotherapy profession, pacing self-management techniques and pain neurophysiology education are indicated for the treatment of musculoskeletal pain in CFS patients. Studies examining the effectiveness of these strategies for CFS patients are warranted. © 2006 Elsevier Ltd. All rights reserved.

Nijs J., Van De Velde B., De Meirleir K.

Pain in patients with chronic fatigue syndrome: Does nitric oxide trigger central sensitisation?

2005 Medical Hypotheses 64 (3); 558 - 562

<http://www.scopus.com/inward/record.url?eid=2-s2.0-11144273881&partnerID=40>

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Previous studies have provided evidence supportive of the clinical importance of widespread pain in patients with chronic fatigue syndrome (CFS): pain severity may account for 26-34% of the variability in the CFS patient's activity limitations and participation restrictions. The etiology of widespread pain in CFS remains to be elucidated, but sensitisation of the central nervous system has been suggested to take part of CFS pathophysiology. It is hypothesised that a nitric oxide (NO) - dependent reduction in inhibitory activity of the central nervous system and consequent central sensitisation accounts for chronic widespread pain in CFS patients. In CFS patients, deregulation of the 2',5'-oligoadenylate synthetase/RNase L pathway is accompanied by activation of the protein kinase R enzyme. Activation of the protein kinase R and subsequent nuclear factor- κ B activation might account for the increased production of NO, while infectious agents frequently associated with CFS (Coxsackie B virus, Epstein-Barr Virus, Mycoplasma) might initiate or accelerate this process. In addition, the evidence addressing behavioural changes in CFS patients fits the central sensitisation-hypothesis: catastrophizing, avoidance behaviour, and somatization may result in, or are initiated by sensitisation of the central nervous system. © 2004 Elsevier Ltd. All rights reserved.

Baraniuk J.N., Petrie K.N., Le U., Tai C.-F., Park Y.-J., Yuta A., Ali M., VandenBussche C.J., Nelson B.
Neuropathology in rhinosinusitis

2005 American Journal of Respiratory and Critical Care Medicine 171 (1); 5 – 11
<http://www.scopus.com/inward/record.url?eid=2-s2.0-11144225841&partnerID=40>

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Pathophysiologic differences in neural responses to hypertonic saline (HTS) were investigated in subjects with acute sinusitis (n = 25), subjects with chronic fatigue syndrome (CFS) with nonallergic rhinitis (n = 14), subjects with active allergic rhinitis (AR; n = 17), and normal (n = 20) subjects. Increasing strengths of HTS were sprayed into their nostrils at 5-minute intervals. Sensations of nasal pain, blockage, and drip increased with concentration and were significantly elevated above normal. These parallels suggested activation of similar subsets of afferent neurons. Urea and lysozyme secretion were dose dependent in all groups, suggesting that serous cell exocytosis was one source of urea after neural stimulation. Only AR and normal groups had mucin dose responses and correlations between symptoms and lysozyme secretion ($R^2 = 0.12-0.23$). The lysozyme dose responses may represent axon responses in these groups. The neurogenic stimulus did not alter albumin (vascular) exudation in any group. Albumin and mucin concentrations were correlated in sinusitis, suggesting that nonneurogenic factors pre-dominated in sinusitis mucous hypersecretion. CFS had neural hypersensitivity (pain) but reduced serous cell secretion. HTS nasal provocations identified significant, unique patterns of neural and mucosal dysregulation in each rhinosinusitis syndrome.

Whiteside A., Hansen S., Chaudhuri A.
Exercise lowers pain threshold in chronic fatigue syndrome

2004 Pain 109 (3); 497 - 499
<http://www.scopus.com/inward/record.url?eid=2-s2.0-2442519505&partnerID=40>

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Post-exertional muscle pain is an important reason for disability in patients who are diagnosed to have Chronic Fatigue Syndrome (CFS). We compared changes in pain threshold in five CFS patients with five age and sex matched controls following graded exercise. Pain thresholds, measured in the skin web between thumb and index finger, increased in control subjects with exercise while it decreased in the CFS subjects. Increased perception of pain and/or fatigue after exercise may be indicative of a dysfunction of the central anti-nociceptive mechanism in CFS patients. © 2004 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Richards R.S., McGregor N.R., Roberts T.K.
Association between oxidative damage markers and self-reported temporomandibular dysfunction symptoms in patients with chronic fatigue syndrome

2004 Journal of Chronic Fatigue Syndrome 12 (3); 45 – 61
<http://www.scopus.com/inward/record.url?eid=2-s2.0-28844481022&partnerID=40>

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Full blood counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), haematinics and markers for oxidative stress were measured on thirty-three patients diagnosed with chronic fatigue

syndrome (CFS) and twenty-seven age and sex matched controls. The CFS patients had increased prevalence of symptoms of temporomandibular dysfunction (TMD). Jaw muscle pain was associated with increases in methaemoglobin ($P < .002$), ferritin ($P < .02$) and malondialdehyde ($P < .007$) whilst temporomandibular joint (TMJ) clicking and/or locking was associated with increases in methaemoglobin ($P < .001$), malondialdehyde ($P < .05$) and vitamin B12 ($P < .02$) levels. Multiple regression analysis found methaemoglobin to be the principle component associated with TMD symptoms in the CFS patients. Increases in scalar severity responses to jaw muscle pain and TMJ clicking and/or locking were positively correlated with methaemoglobin by multiple regression. These data indicate that oxidative stress due to excess free radical formation was associated with jaw muscle pain in CFS patients and suggest that these symptoms were likely to be associated with a pathogen-associated aetiology. © 2004 by The Haworth Press, Inc. All rights reserved.

Nijs J., Vanherberghen K., Duquet W., De Meirleir K.

Chronic fatigue syndrome: Lack of association between pain-related fear of movement and exercise capacity and disability

2004 Physical Therapy 84 (8); 696 - 705

<http://www.scopus.com/inward/record.url?eid=2-s2.0-3342981117&partnerID=40>

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Background and Purpose. Patients who experience pain, a symptom of chronic fatigue syndrome (CFS), often exhibit kinesiophobia (irrational fear of movement). The purpose of this study was to examine whether pain-related fear of movement is associated with exercise capacity, activity limitations, or participation restrictions in patients with CFS who experience widespread pain. **Subjects and Methods.** Sixty-four subjects met the inclusion criteria. All subjects fulfilled the 1994 Centers for Disease Control and Prevention case definition for CFS and experienced widespread myalgias or arthralgias. The subjects completed the Tampa Scale for Kinesiophobia-Dutch Version (TSK-DV) and the Dutch Chronic Fatigue Syndrome-Activities and Participation Questionnaire (CFS-APQ). They then performed a maximal exercise test on a bicycle ergometer. Heart rate was monitored continuously by use of an electrocardiograph. Ventilatory factors were measured through spirometry. Correlations between the TSK-DV scores and both the exercise capacity data and the CFS-APQ scores were assessed using the Spearman rank correlation coefficient. Using the Mann-Whitney U test, the TSK-DV scores were compared between subjects who performed a maximal exercise stress test and those who did not perform the test. **Results.** Forty-seven subjects (73.4%) attained a total score of greater than 37 on the TSK-DV, indicating high fear of movement. Neither the exercise capacity data nor the CFS-APQ scores indicated a correlation with the TSK-DV scores ($n=64$). Subjects who did not perform a maximal exercise capacity test had more fear of movement (median TSK-DV score=43.0, interquartile range=10.3) compared with those who did perform a maximal exercise capacity test (median TSK-DV score=38.0, interquartile range=13.2; Mann-Whitney U-test score=322.5, $z=-1.974$, $P=.048$), but the correlation analysis was unable to reveal an association between exercise capacity and kinesiophobia in either subgroup. **Discussion and Conclusion.** These results indicate a lack of correlation between kinesiophobia and exercise capacity, activity limitations, or participation restrictions, at least in patients with CFS who are experiencing widespread muscle or joint pain.

Nijs J., De Meirleir K., Truyen S.

Hypermobility in patients with chronic fatigue syndrome: Preliminary observations

2004 Journal of Musculoskeletal Pain 12 (1); 9 – 17

<http://www.scopus.com/inward/record.url?eid=2-s2.0-3042594458&partnerID=40>

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Objective: The present report aims at examining 1, the prevalence of generalized hypermobility in patients with chronic fatigue syndrome [CFS]; 2, whether hypermobile CFS patients experience more pain and have more severe activity limitations/participation restrictions compared to nonhypermobile CFS patients; and 3, whether the history of widespread pain is indicative of generalized hypermobility in patients with CFS. Methods: Forty-four consecutive patients with CFS filled in the Chronic Fatigue Syndrome Activities and Participation Questionnaire [CFS-APQ] for the assessment of activity limitations/participation restrictions, rated three visual analog scales [for pain, myalgia, and arthralgia], were screened for generalized hypermobility according to the Beighton et al. (1973) criteria, and were questioned about muscle and joint aches. Results: Eleven of the 44 [25 percent] subjects met the for generalized hypermobility. The Spearman Rank correlation analysis did not reveal statistically significant correlations between the Beighton et al. scores and any of the self-reported measures [$P > 0.011$]. Using the Mann-Whitney U test, no statistically significant differences in pain severity and activity limitations/participation restrictions were observed between hypermobile [$N = 11$] and nonhypermobile [$N = 33$] patients with CFS [$P > 0.01$]. The positive likelihood ratio for widespread pain in shifting the odds favoring the presence of generalized hypermobility was 1.24; the negative likelihood ratio was 0.749. Conclusions: The present report suggests that a subgroup of patients with CFS present with generalized hypermobility, but questions the clinical importance of hypermobility in patients with CFS. A history of widespread pain was not predictive of generalized hypermobility in this sample of CFS patients. © 2004 by The Haworth Press, Inc. All rights reserved.

Metcalf L.N., McGregor N.R., Roberts T.K.

Membrane damaging toxins from coagulase-negative Staphylococcus are associated with self-reported temporomandibular disorder (TMD) in patients with chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-28844469420&partnerID=40>

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Objective: To assess whether there is any association between membrane damaging toxin production by Staphylococcus spp. and self-reported TMD symptom expression in a group of patients selected to have CFS. Methods: Thirty-three defined Chronic Fatigue Syndrome (CFS) patients and 33 age- and sex-matched controls were assessed to evaluate the relationship between carriage of membrane damaging toxin producing Staphylococcus, CFS and temporomandibular dysfunction (TMD) symptoms. Results: The CFS patients had an increased prevalence of face pain (Odds Ratio = 21.0, 95% CL 4.2-106, $P < .001$) and temporomandibular joint (TMJ) clicking/locking (OR = 5.7, 95% CL 1.4- 23.5, $P < .007$), and the coagulase-negative Staphylococcus maximum % \hat{I}^2 -toxin haemolysis per patient. Both multivariate and univariate analyses revealed an association between the membrane damaging \hat{I}^1 -toxin producing CoNS (MDT-CoNS) species per subject and face pain prevalence and intensity within both the CFS patients and the control subjects. No association was found between CoNS toxin production and TMJ clicking/locking. Importantly, \hat{I}^{\pm} - and \hat{I}^2 -toxin production by CoNS was associated with patient reporting of arthritis. Conclusions: These data confirm the original observations of the association between MDT-CoNS and facial muscle pain (Butt et al., 1998; McGregor et al., 2003).

These data also suggest that MDT-CoNS associated facial muscle pain expression represents a distinct clinical entity, which has an increased prevalence in CFS patients. © 2004 by The Haworth Press, Inc. All rights reserved.

Gerwin R.
Differential diagnosis of trigger points

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33644674715&partnerID=40>

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Objective: A number of medical and structural conditions produce muscular pain associated with myofascial trigger points [TrPs]. These conditions should be considered when evaluating a patient with muscle pain. Thesis: Myofascial pain syndrome is characterized by regional or widespread myalgia with muscle TrPs. Trigger points are also common in fibromyalgia. The TrP is a physical sign that occurs in a variety of myalgic conditions. Acute or chronic muscle stress creates an "energy crisis" that can result in a TrP. A muscle-related nociceptive stimulation of the peripheral and central nervous system results in hypersensitivity. Both mechanical and systemic medical disorders stress muscle. Mechanical problems can be structural or postural. Static [postural] or acute [trauma] muscle overload occurs in mechanical disorders which results in physical and biochemical changes including hypoxia and ischemia, and neuromuscular junction dysfunction. Delayed onset muscle pain is seen in unaccustomed eccentric exercise. Post-laminectomy and failed spinal fusions are causes of myofascial pain syndrome. Systemic medical disorders can result in diffuse TrP-related myalgia, though the mechanism may be unclear. Systemic medical disorders that cause TrP-related pain include connective tissue disorders [hypermobility syndrome and polymyalgia rheumatica], hypothyroidism, vitamin B12 insufficiency, and infectious diseases [Lyme disease and parasitic infection]. Drug induced myalgia ['statin' drugs, propoxyphene, and penicillamine] and myalgic encephalomyelitis/chronic fatigue syndrome, neurogenic myalgia in radiculopathy or nerve entrapment, and viscerosomatic pain syndromes are all important causes. Conclusion: Trigger points pain can have many different causes that must be identified and treated specifically. © 2004 by The Haworth Press, Inc. All rights reserved.

Creavin S.T., Dunn K.M., Mallen C.D., Nijrolder I., van der Windt D.A.W.M.
Co-occurrence and associations of pain and fatigue in a community sample of Dutch adults

European Journal of Pain

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67049157993&partnerID=40>

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Widespread pain and chronic fatigue are common in the general population. Previous research has demonstrated co-occurrence of syndromes that are associated with pain and fatigue (fibromyalgia and chronic fatigue syndrome), but there is limited existing data on the co-occurrence of these symptoms in general. This study investigates the co-occurrence of pain and fatigue, and characterises people with these symptoms individually, and in combination. A postal questionnaire was sent to a random sample of 4741 community dwelling Dutch adults registered with five general practices. There were 2447 participants (adjusted response = 53.5%). Persistent fatigue was reported by 60% of the 451 subjects with chronic widespread pain. Chronic widespread pain was reported by 33% of the 809 responders with persistent fatigue. Anxiety and depression were more common in subjects who reported both symptoms than those who reported either one or neither. Participants who had chronic disease, high body mass index, low activity levels or did not perceive ability to influence health had higher adjusted odds of reporting both symptoms (but not one alone) than subjects not having these characteristics. Pain and fatigue occur more often than would be expected by chance and there are a number of reasons for this. Clinicians should be aware that co-occurrence of the symptoms is common, especially

in people who have high BMI or chronic disease, and that people with both symptoms are often anxious or depressed. Further work should address longitudinal associations of pain and fatigue. © 2009 European Federation of Chapters of the International Association for the Study of Pain.

Sleep

Armitage R., Landis C., Hoffmann R., Lentz M., Watson N., Goldberg J., Buchwald D.
Power spectral analysis of sleep EEG in twins discordant for chronic fatigue syndrome

2009 *Journal of Psychosomatic Research* 66 (1); 51 – 57

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Objective: The purpose of the study was to evaluate quantitative sleep electroencephalogram (EEG) frequencies in monozygotic twins discordant for chronic fatigue syndrome. **Methods:** Thirteen pairs of female twins underwent polysomnography. During the first night, they adapted to the sleep laboratory, and during the second night, their baseline sleep was assessed. Visual stage scoring was conducted on sleep electroencephalographic records according to standard criteria, and power spectral analysis was used to quantify delta through beta frequency bands, processed in 6-s blocks. Data were averaged across sleep stage within each twin and coded for sleep stage and the presence or absence of chronic fatigue syndrome (CFS). A completely within-subjects repeated measure multivariate analysis of variance evaluated twin pairs by frequency band by sleep stage interactions and simple effects. The relationship between alpha and delta EEG was also assessed across twin pairs. **Results:** No significant differences in spectral power in any frequency band were found between those with CFS and their nonfatigued cotwins. Phasic alpha activity, coupled with delta was noted in five subjects with CFS but was also present in 4/5 healthy twins, indicating this finding likely reflects genetic influences on the sleep electroencephalogram rather than disease-specific sleep pathology. **Conclusions:** The genetic influences on sleep polysomnography and microarchitecture appear to be stronger than the disease influence of chronic fatigue syndrome, despite greater subjective sleep complaint among the CFS twins. EEG techniques that focus on short duration events or paradigms that probe sleep regulation may provide a better description of sleep abnormalities in CFS. © 2009 Elsevier Inc. All rights reserved.

Togo F., Natelson B.H., Cherniack N.S., FitzGibbons J., Garcon C., Rapoport D.M.

Sleep structure and sleepiness in chronic fatigue syndrome with or without coexisting fibromyalgia

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-44449130089&partnerID=40>

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Introduction: We evaluated polysomnograms of chronic fatigue syndrome (CFS) patients with and without fibromyalgia to determine whether patients in either group had elevated rates of sleep-disturbed breathing (obstructive sleep apnea or upper airway resistance syndrome) or periodic leg movement disorder. We also determined whether feelings of unrefreshing sleep were associated with differences in sleep architecture from normal. **Methods:** We compared sleep structures and subjective scores on visual analog scales for sleepiness and fatigue in CFS patients with or without coexisting fibromyalgia (n = 12 and 14, respectively) with 26 healthy subjects. None had current major depressive disorder, and all were studied at the same menstrual phase. **Results:** CFS patients had

significant differences in polysomnographic findings from healthy controls and felt sleepier and more fatigued than controls after a night's sleep. CFS patients as a group had less total sleep time, lower sleep efficiency, and less rapid eye movement sleep than controls. A possible explanation for the unrefreshing quality of sleep in CFS patients was revealed by stratification of patients into those who reported more or less sleepiness after a night's sleep (a.m. sleepier or a.m. less sleepy, respectively). Those in the sleepier group reported that sleep did not improve their symptoms and had poorer sleep efficiencies and shorter runs of sleep than both controls and patients in the less sleepy group; patients in the less sleepy group reported reduced fatigue and pain after sleep and had relatively normal sleep structures. This difference in sleep effects was due primarily to a decrease in the length of periods of uninterrupted sleep in the a.m. sleepier group. Conclusion: CFS patients had significant differences in polysomnographic findings from healthy controls and felt sleepier and more fatigued than controls after a night's sleep. This difference was due neither to diagnosable sleep disorders nor to coexisting fibromyalgia but primarily to a decrease in the length of periods of uninterrupted sleep in the patients with more sleepiness in the morning than on the night before. This sleep disruption may explain the overwhelming fatigue, report of unrefreshing sleep, and pain in this subgroup of patients. © 2008 Togo et al.; licensee BioMed Central Ltd.

Ohinata J., Suzuki N., Araki A., Takahashi S., Fujieda K., Tanaka H.
Actigraphic assessment of sleep disorders in children with chronic fatigue syndrome

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Children with chronic fatigue syndrome (CFS) often suffer from sleep disorders, which cause many physiological and psychological problems. Understanding sleep characteristics in children with CFS is important for establishing a therapeutic strategy. We conducted an actigraphic study to clarify the problems in sleep/wake rhythm and physical activity in children with CFS. Methods. Actigraphic recordings were performed for 1-2 weeks in 12 CFS children. The obtained data were compared with those of healthy age-matched children used as the control. Results. Sleep patterns were divided into two groups based on subjects' sleep logs: irregular sleep type and delayed sleep phase type. Compared to the control group, total sleep time was longer and physical activity was lower in both groups of CFS. Continuous sleep for more than 10 h was not uncommon in CFS. In the irregular sleep type, impaired daily sleep/wake rhythms and disrupted sleep were observed. Conclusion. Using actigraphy, we could identify several characteristics of the sleep patterns in CFS children. Actigraphic analysis proved to be useful in detecting sleep/wake problems in children with CFS. © 2007 Elsevier B.V. All rights reserved.

Neu D., Hoffmann G., Moutrier R., Verbanck P., Linkowski P., Le Bon O.
Are patients with chronic fatigue syndrome just 'tired' or also 'sleepy'?

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It is presently unclear whether chronic fatigue syndrome (CFS) patients exhibit daytime sleepiness in addition to fatigue. Both, fatigue, such as that seen in CFS patients, and excessive daytime sleepiness, such as in sleep apnea-hypopnea syndrome (SAHS), remain poorly understood. Both daytime

conditions are generally related to unrefreshing sleep and show affective symptoms. This study's objective was to contribute to the understanding of the relationship between fatigue and sleepiness in CFS patients not co-morbid for primary sleep or psychiatric disorders. We compared 16 untreated CFS patients (mean age 32.8, all females) with 13 untreated SAHS (mean age 47.7, all females) patients and 12 healthy controls (mean age 32.2, all females). Objective sleepiness was measured using multiple sleep latency tests (MSLT). Subjective sleepiness and fatigue were assessed with the Epworth Sleepiness Scale and the Fatigue Severity Scale, respectively. Mean Sleep Latency (SL) on the MSLT was significantly shorter in SAHS patients than in CFS patients and CFS patients showed significantly shorter mean SL than matched controls but within normal range. Subjective sleepiness was greatest in SAHS patients and subjective fatigue was highest in CFS patients. Affective symptoms showed highest intensities in CFS patients. While higher than the control group on all measures, compared to SAHS, the CFS group had higher subjective fatigue and lower subjective and objective sleepiness. Despite possible overlap in symptoms and signs of both daytime conditions, our data indirectly support the clinical distinction between fatigue and sleepiness. © 2008 European Sleep Research Society.

Le Bon O., Neu D., Valente F., Linkowski P.

Paradoxical NREMS distribution in "pure" chronic fatigue patients a comparison with sleep apnea-hypopnea patients and healthy control subjects

2008 Journal of Chronic Fatigue Syndrome 14 (2); 45 – 59

<http://www.scopus.com/inward/record.url?eid=2-s2.0-39049152293&partnerID=40>

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Objective: The chronic fatigue syndrome (CFS) is a debated clinical entity, not presently associated with specific sleep abnormalities. However, higher levels of deep sleep and/or lower levels of light sleep have been reported in several all-night polysomnography studies in CFS patients. This distribution of Non-Rapid Eye Movement Sleep (NREMS) contrasts with what would be expected if sleep was interrupted by microawakenings, such as in sleep apneas or periodic limb movements, where more light sleep and less deep sleep are commonly observed. This "paradoxical" distribution of NREMS could represent a characteristic feature of chronic fatigue and deserved to be investigated. Methods: A retrospective comparison of the NREMS distribution was performed between 28 "pure" Chronic Fatigue Syndrome patients (without primary sleep or psychiatric disorders), 27 Apneic-Hypopneic patients and 27 Healthy Controls. Results: Data showed CFS patients to have a higher stage 4/stage 2 or stage 4/light sleep ratios than the other two conditions. Conclusion: This sleep pattern is closer to what is observed in cases of infections than to what is seen after sleep fragmentation by primary sleep or in psychiatric disorders. Such a particular sleep pattern could provide insights into the pathophysiology of fatigue. Copyright © by The Haworth Press, Inc. All rights reserved.

Kishi A., Struzik Z.R., Natelson B.H., Togo F., Yamamoto Y.

Dynamics of sleep stage transitions in healthy humans and patients with chronic fatigue syndrome

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Physiological and/or pathological implications of the dynamics of sleep stage transitions have not, to date, been investigated. We report detailed duration and transition statistics between sleep stages in healthy subjects and in others with chronic fatigue syndrome (CFS); in addition, we also compare our data with previously published results for rats. Twenty-two healthy females and 22 female patients with CFS, characterized by complaints of unrefreshing sleep, underwent one night of polysomnographic recording. We find that duration of deep sleep (stages III and IV) follows a power-law probability distribution function; in contrast, stage II sleep durations follow a stretched exponential and stage I, and REM sleep durations follow an exponential function. These stage duration distributions show a gradually increasing departure from the exponential form with increasing depth of sleep toward a power-law type distribution for deep sleep, suggesting increasing complexity of regulation of deeper sleep stages. We also find a substantial number of REM to non-REM sleep transitions in humans, while this transition is reported to be virtually nonexistent in rats. The relative frequency of this REM to non-REM sleep transition is significantly lower in CFS patients than in controls, resulting in a significantly greater relative transition frequency of moving from both REM and stage I sleep to awake. Such an alteration in the transition pattern suggests that the normal continuation of sleep in light or REM sleep is disrupted in CFS. We conclude that dynamic transition analysis of sleep stages is useful for elucidating yet-to-be-determined human sleep regulation mechanisms with pathophysiological implications. Copyright © 2008 the American Physiological Society.

Van Hoof E., De Becker P., Lapp C., Cluydts R., De Meirleir K.

Defining the occurrence and influence of alpha-delta sleep in chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847076425&partnerID=40>

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BACKGROUND: Patients with chronic fatigue syndrome (CFS) present a disordered sleep pattern and frequently undergo polysomnography to exclude a primary sleep disorder. Such studies have shown reduced sleep efficiency, a reduction of deep sleep, prolonged sleep initiation, and alpha-wave intrusion during deep sleep. Deregulation of the 2-5A synthetase/RNase L antiviral pathway and a potential acquired channelopathy are also found in a subset of CFS patients and could lead to sleep disturbances. This article compiles a large sleep study database on CFS patients and correlates these data with a limited number of immune parameters as it has been thought that RNase L could be associated with these sleep disturbances. **METHODS:** Forty-eight patients who fulfilled 1994 Centers for Disease Control and Prevention criteria for CFS underwent extensive medical evaluation, routine laboratory testing, and a structured psychiatric interview. Subjects then completed a complaint checklist and a two-night polysomnographic investigation. RNase L analysis was performed by gel electrophoresis using a radiolabeled 2⁵A²-oligoadenylate trimer. Basic descriptive statistical parameters were calculated. **RESULTS:** Patients experienced a prolonged sleep latency, showed a low sleep efficiency index, and had a low percentage of slow wave sleep. The present alpha-delta intrusion correlated with anxiety; no correlations appeared, however, between alpha-delta sleep and immunologic parameters, including RNase L. **CONCLUSIONS:** The main findings are 1) validation of sleep latency problems and

other sleep disturbances as already suggested by several authors; 2) alpha-delta intrusion seems associated with anxiety; and 3) elevated RNase L did not correlate with alpha-delta sleep. © Copyright 2007 Southern Society for Clinical Investigation.

Neu D., Mairesse O., Hoffmann G., Dris A., Lambrecht L.J., Linkowski P., Verbanck P., Le Bon O.
Sleep quality perception in the chronic fatigue syndrome: Correlations with sleep efficiency, affective symptoms and intensity of fatigue

2007 Neuropsychobiology 56 (1); 40 - 46

<http://www.scopus.com/inward/record.url?eid=2-s2.0-36348932212&partnerID=40>

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Background/Aims: One of the core symptoms of the chronic fatigue syndrome (CFS) is unrefreshing sleep and a subjective sensation of poor sleep quality. Whether this perception can be expressed, in a standardized questionnaire as the Pittsburgh Sleep Quality Index (PSQI), has to our knowledge never been documented in CFS. Furthermore, correlations of subjective fatigue, PSQI, affective symptoms and objective parameters such as sleep efficiency are poorly described in the literature. Methods: Using a cross-sectional paradigm, we studied subjective measures like PSQI, Fatigue Severity Scale scores and intensity of affective symptoms rated by the Hamilton Depression and Anxiety scales as well as objective sleep quality parameters measured by polysomnography of 28 'pure' (no primary sleep and no psychiatric disorders) CFS patients compared to age- and gender-matched healthy controls. Results: The PSQI showed significantly poorer subjective sleep quality in CFS patients than in healthy controls. In contrast, objective sleep quality parameters, like the Sleep Efficiency Index (SEI) or the amount of slow-wave sleep did not differ significantly. Subjective sleep quality showed a correlation trend with severity of fatigue and was not correlated with the intensity of affective symptoms in CFS. Conclusion: Our findings indicate that a sleep quality misperception exists in CFS or that potential nocturnal neurophysiological disturbances involved in the nonrecovering sensation in CFS are not expressed by sleep variables such as the SEI or sleep stage distributions and proportions. Copyright © 2007 S. Karger AG.

Martin A., Chalder T., Rief W., Braehler E.

The relationship between chronic fatigue and somatization syndrome: A general population survey

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-34447633344&partnerID=40>

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Objective: The objective of this study was to assess the prevalence of chronic fatigue (CF) and its association with somatization syndrome [Somatization Syndrome Index (SSI) 4/6: 4 somatoform symptoms in men, 6 in women] in the general population. Methods: A representative sample of the German population (N=2412) completed a fatigue questionnaire and a screening instrument for current somatoform symptoms (Screening for Somatoform Symptoms 7). Results: The prevalence rate of CF was 6.1% (n=147). Females were affected significantly more often as compared with males (7% vs. 5.1%). The mean number of somatoform symptoms was higher in CF cases than in control subjects without CF (11 vs. 2; P<.001). Seventy-two percent of the subjects with CF fulfilled the SSI4/6 criterion for somatization syndrome. Quality of life (EUROHIS-QOL and 8-item Short-Form Health Survey) and well-being (5-item WHO Well-Being Index) were markedly decreased in CF and SSI4/6.

The results of regression analyses suggest that fatigue and somatization severity had a similar impact on quality of life. Conclusions: The results suggest that CF is relevant in the general population. Its substantial overlap with somatization syndrome supports the hypothesis that the two syndromes are only partially different manifestations of the same underlying processes. © 2007 Elsevier Inc. All rights reserved.

Majer M., Jones J.F., Unger E.R., Youngblood L.S., Decker M.J., Gurbaxani B., Heim C., Reeves W.C.
Perception versus polysomnographic assessment of sleep in CFS and non-fatigued control subjects:
Results from a population-based study

2007 BMC Neurology 7

<http://www.scopus.com/inward/record.url?eid=2-s2.0-39049088988&partnerID=40>

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Background: Complaints of unrefreshing sleep are a prominent component of chronic fatigue syndrome (CFS); yet, polysomnographic studies have not consistently documented sleep abnormalities in CFS patients. We conducted this study to determine whether alterations in objective sleep characteristics are associated with subjective measures of poor sleep quality in persons with CFS. Methods: We examined the relationship between perceived sleep quality and polysomnographic measures of nighttime and daytime sleep in 35 people with CFS and 40 non-fatigued control subjects, identified from the general population of Wichita, Kansas and defined by empiric criteria. Perceived sleep quality and daytime sleepiness were assessed using clinical sleep questionnaires. Objective sleep characteristics were assessed by nocturnal polysomnography and daytime multiple sleep latency testing. Results: Participants with CFS reported unrefreshing sleep and problems sleeping during the preceding month significantly more often than did non-fatigued controls. Participants with CFS also rated their quality of sleep during the overnight sleep study as significantly worse than did control subjects. Control subjects reported significantly longer sleep onset latency than latency to fall asleep as measured by PSG and MSLT. There were no significant differences in sleep pathology or architecture between subjects with CFS and control subjects. Conclusion: People with CFS reported sleep problems significantly more often than control subjects. Yet, when measured these parameters and sleep architecture did not differ between the two subject groups. A unique finding requiring further study is that control, but not CFS subjects, significantly over reported sleep latency suggesting CFS subjects may have an increased appreciation of sleep behaviour that may contribute to their perception of sleep problems. © 2007 Majer et al; licensee BioMed Central Ltd.

Armitage R., Landis C., Hoffmann R., Lentz M., Watson N.F., Goldberg J., Buchwald D.
The impact of a 4-hour sleep delay on slow wave activity in twins discordant for chronic fatigue syndrome

2007 Sleep 30 (5); 657 - 662

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34250659234&partnerID=40>

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Objectives: Chronic fatigue syndrome (CFS) has been associated with altered amounts of slow wave sleep, which could reflect reduced delta electroencephalograph (EEG) activity and impaired sleep regulation. To evaluate this hypothesis, we examined the response to a sleep regulatory challenge in CFS. Design: The first of 3 consecutive nights of study served as laboratory adaptation. Baseline sleep

was assessed on the second night. On the third night, bedtime was delayed by 4 hours, followed by recovery sleep. Total available sleep time was held constant on all nights. Setting: A research sleep laboratory. Participants: 13 pairs of monozygotic twins discordant for CFS. Interventions: N/A Measurements and Results: Power spectral analysis quantified slow wave activity (SWA) in the 0.5-3.9 Hz band in successive NREM periods (stage 2, 3, or 4) on each night. To ensure comparability, analyses were restricted to the first 4 NREM periods on each night. Data were coded for NREM period and twin pair. Repeated-measures analysis of variance (ANOVA) contrasted sleep delay effects across NREM periods between twin pairs. A second ANOVA calculated the SWA in each NREM period in recovery sleep relative to baseline SWA. The 2 groups of twins were similar on baseline SWA power. After sleep delay, CFS twins exhibited significantly less SWA power in the first NREM period of recovery sleep and accumulated a smaller percentage of SWA in the first NREM period than their co-twins. Conclusions: CFS is associated with a blunted SWA response to sleep challenge, suggesting that the basic sleep drive and homeostatic response are impaired.

Reeves W.C., Heim C., Maloney E.M., Youngblood L.S., Unger E.R., Decker M.J., Jones J.F., Rye D.B. Sleep characteristics of persons with chronic fatigue syndrome and non-fatigued controls: Results from a population-based study

2006 BMC Neurology 6

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33845245670&partnerID=40>

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Background: The etiology and pathophysiology of chronic fatigue syndrome (CFS) remain inchoate. Attempts to elucidate the pathophysiology must consider sleep physiology, as unrefreshing sleep is the most commonly reported of the 8 case-defining symptoms of CFS. Although published studies have consistently reported inefficient sleep and documented a variable occurrence of previously undiagnosed primary sleep disorders, they have not identified characteristic disturbances in sleep architecture or a distinctive pattern of polysomnographic abnormalities associated with CFS. Methods: This study recruited CFS cases and non-fatigued controls from a population based study of CFS in Wichita, Kansas. Participants spent two nights in the research unit of a local hospital and underwent overnight polysomnographic and daytime multiple sleep latency testing in order to characterize sleep architecture. Results: Approximately 18% of persons with CFS and 7% of asymptomatic controls were diagnosed with severe primary sleep disorders and were excluded from further analysis. These rates were not significantly different. Persons with CFS had a significantly higher mean frequency of obstructive apnea per hour ($p = .003$); however, the difference was not clinically meaningful. Other characteristics of sleep architecture did not differ between persons with CFS and controls. Conclusion: Although disordered breathing during sleep may be associated with CFS, this study generally did not provide evidence that altered sleep architecture is a critical factor in CFS. Future studies should further scrutinize the relationship between subjective sleep quality relative to objective polysomnographic measures. © 2006 Reeves et al; licensee BioMed Central Ltd.

Guilleminault C., Poyares D., Rosa A.d., Kirisoglu C., Almeida T., Lopes M.C. Chronic fatigue, unrefreshing sleep and nocturnal polysomnography

2006 Sleep Medicine 7 (6); 513 - 520

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33748030454&partnerID=40>

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Background and purpose: To investigate the complaint of unrefreshing sleep with study of sleep electroencephalogram (EEG) in patients with chronic fatigue. Patients and methods: Fourteen

successively seen patients (mean age: 41.1 ± 9.8) who complained of chronic fatigue but denied sleepiness and agreed to participate were compared to 14 controls (33.6 ± 10.2 years) who were monitored during sleep recorded in parallel. After performing conventional sleep scoring we applied Fast Fourier Transformation (FFT) for the delta 1, delta 2, theta, alpha, sigma 1, sigma 2, beta EEG frequency bands. The presence of non-rapid eye movement (NREM) sleep instability was studied with calculation of cyclic alternating pattern (CAP) rate. Two-way analysis of variance (ANOVA) was performed to analyze FFT results and Mann-Whitney U-test to compare CAP rate in both groups of subjects. Results: Slow wave sleep (SWS) percentage and sleep efficiency were lower, but there was a significant increase in delta 1 (slow delta) relative power in the chronic fatigue group when compared to normals ($P < 0.01$). All the other frequency bands were proportionally and significantly decreased compared to controls. CAP rate was also significantly greater in subjects with chronic fatigue than in normals ($P = 0.04$). An increase in respiratory effort and nasal flow limitation were noted with chronic fatigue. Conclusions: The complaints of chronic fatigue and unrefreshing sleep were associated with an abnormal CAP rate, with increase in slow delta power spectrum, affirming the presence of an abnormal sleep progression and NREM sleep instability. These specific patterns were related to subtle, undiagnosed sleep-disordered breathing. © 2006 Elsevier B.V. All rights reserved.

Randall D.C., Cafferty F.H., Shneerson J.M., Smith I.E., Llewelyn M.B., File S.E.
Chronic treatment with modafinil may not be beneficial in patients with chronic fatigue syndrome
2005 Journal of Psychopharmacology 19 (6); 647 – 660
<http://www.scopus.com/inward/record.url?eid=2-s2.0-27644571512&partnerID=40>

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Fourteen patients (7 male, 7 female, 22-63 years), classified as having chronic fatigue syndrome (CFS), but without concurrent major depression, significant sleepiness or use of psychoactive medication, completed a double-blind, placebo-controlled, crossover study of the effects of the selective wakefulness-promoting agent, modafinil (200 and 400mg/day). The treatment periods were each 20 days, with washout periods of 2 weeks. The primary aim was to determine effects on cognition and the secondary aim was to determine effects on self-ratings of fatigue, quality of life and mood. Modafinil had mixed effects in two cognitive tasks. In a test of sustained attention, treatment with 200 mg reduced the latency to correctly detect sequences, but 400 mg increased the number of missed targets. In a test of spatial planning, the 200 mg dose resulted in a slower initial thinking time for the easiest part of the task, whereas 400 mg reduced the initial thinking time for the hardest part of the test. Lastly, in a test of mental flexibility and one of motor speed, patients performed worse whilst on modafinil (400 mg), compared with the placebo period. No effects were observed on the performance of other psychometric tests or on self-ratings of fatigue, quality of life or mood, but this may have been due to insufficient statistical power. It is discussed whether the limited and mixed cognitive effects that we observed could have occurred by chance, or whether a subgroup of CFS patients with daytime sleepiness would have shown greater benefits. © 2005 British Association for Psychopharmacology.

Watson N.F., Jacobsen C., Goldberg J., Kapur V., Buchwald D.
Subjective and objective sleepiness in monozygotic twins discordant for chronic fatigue syndrome

2004 Sleep 27 (5); 973 - 977

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4143054734&partnerID=40>

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Study Objective: To examine the association of chronic fatigue syndrome (CFS) with measures of objective and subjective sleepiness. **Design:** Monozygotic co-twin control study. **Setting:** Academic medical center. **Patients and Participants:** Twenty monozygotic twin pairs discordant for CFS. **Interventions:** N/A. **Measurements and Results:** All twins completed an Epworth Sleepiness Scale (ESS), 4 Stanford Sleepiness Scales (SSS), and underwent a standard 4-nap multiple sleep latency test. We compared the ESS scores, average SSS scores, and average sleep latency in CFS and healthy twins. The CFS twins reported more sleepiness as measured by mean scores on the ESS (10.9 vs 8.2; 95% confidence interval [CI] = 0.3-5.5; $P = .03$) and the SSS (3.4 versus 2.1; 95% CI = 0.7-1.9; $P < .001$). The mean sleep latency on the Multiple Sleep Latency Test was not significantly different between the CFS and healthy twins (8.9 vs 10.0 minutes; 95% CI -4.4-1.7; $P = .33$). Mean SSS scores increased among the CFS twins and decreased among healthy twins from nap 1 to nap 4 ($P < .001$). The individual ESS scores and mean sleep latencies on the Multiple Sleep Latency Test were negatively correlated for all the twins (Pearson's $r = -0.40$; $P = .01$), with a slightly stronger association among the healthy twins (Pearson's $r = -0.42$, $P = .07$) than the CFS twins (Pearson's $r = -0.36$, $P = .15$). **Conclusions:** CFS twins reported significantly more subjective sleepiness than their healthy co-twins despite similar nonpathologic mean sleep latencies on the Multiple Sleep Latency Test. Patients with CFS may mistake their chronic disabling fatigue for sleepiness.

Unger E.R., Nisenbaum R., Moldofsky H., Cesta A., Sammut C., Reyes M., Reeves W.C.
Sleep assessment in a population-based study of chronic fatigue syndrome

2004 BMC Neurology 4

<http://www.scopus.com/inward/record.url?eid=2-s2.0-2642544211&partnerID=40>

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Background. Chronic fatigue syndrome (CFS) is a disabling condition that affects approximately 800,000 adult Americans. The pathophysiology remains unknown and there are no diagnostic markers or characteristic physical signs or laboratory abnormalities. Most CFS patients complain of unrefreshing sleep and many of the postulated etiologies of CFS affect sleep. Conversely, many sleep disorders present similarly to CFS. Few studies characterizing sleep in unselected CFS subjects have been published and none have been performed in cases identified from population-based studies. **Methods.** The study included 339 subjects (mean age 45.8 years, 77% female, 94.1% white) identified through telephone screen in a previously described population-based study of CFS in Wichita, Kansas. They completed questionnaires to assess fatigue and wellness and 2 self-administered sleep questionnaires. Scores for five of the six sleep factors (insomnia/hypersomnia, non-restorative sleep, excessive daytime somnolence, sleep apnea, and restlessness) in the Centre for Sleep and Chronobiology's Sleep Assessment Questionnaire[®] (SAQ[®]) were dichotomized based on threshold. The Epworth Sleepiness Scale score was used as a continuous variable. **Results.** 81.4% of subjects had an abnormality in at least one SAQ[®] sleep factor. Subjects with sleep factor abnormalities had significantly lower wellness scores but statistically unchanged fatigue severity scores compared to those without SAQ[®] abnormality. CFS subjects had significantly increased risk of abnormal scores in the non-restorative (adjusted odds ratio [OR] = 28.1; 95% confidence interval [CI] = 7.4-107.0) and restlessness (OR = 16.0; 95% CI = 4.2-61.6) SAQ[®] factors compared to non-fatigued, but not for

factors of sleep apnea or excessive daytime somnolence. This is consistent with studies finding that, while fatigued, CFS subjects are not sleepy. A strong correlation (0.78) of Epworth score was found only for the excessive daytime somnolence factor. Conclusions. SAQ[®] factors describe sleep abnormalities associated with CFS and provide more information than the Epworth score. Validation of these promising results will require formal polysomnographic sleep studies. © 2004 Unger et al, licensee BioMed Central Ltd.

Fossey M., Libman E., Bailes S., Baltzan M., Schondorf R., Amsel R., Fichten C.S.
Sleep quality and psychological adjustment in chronic fatigue syndrome

2004 Journal of Behavioral Medicine 27 (6); 581 – 591

<http://www.scopus.com/inward/record.url?eid=2-s2.0-15744363760&partnerID=40>

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Without specific etiology or effective treatment, chronic fatigue syndrome (CFS) remains a contentious diagnosis. Individuals with CFS complain of fatigue and poor sleep-symptoms that are often attributed to psychological disturbance. To assess the nature and prevalence of sleep disturbance in CFS and to investigate the widely presumed presence of psychological maladjustment we examined sleep quality, sleep disorders, physical health, daytime sleepiness, fatigue, and psychological adjustment in three samples: individuals with CFS; a healthy control group; and individuals with a definite medical diagnosis: narcolepsy. Outcome measures included physiological evaluation (polysomnography), medical diagnosis, structured interview, and self-report measures. Results indicate that the CFS sample had a very high incidence (58%) of previously undiagnosed primary sleep disorder such as sleep apnea/hypopnea syndrome and restless legs/periodic limb movement disorder. They also had very high rates of self-reported insomnia and nonrestorative sleep. Narcolepsy and CFS participants were very similar on psychological adjustment: both these groups had more psychological maladjustment than did control group participants. Our data suggest that primary sleep disorders in individuals with CFS are underdiagnosed in primary care settings and that the psychological disturbances seen in CFS may well be the result of living with a chronic illness that is poorly recognized or understood. © 2004 Springer Science+Business Media, Inc.

Ball N., Buchwald D.S., Schmidt D., Goldberg J., Ashton S., Armitage R.

Monozygotic twins discordant for chronic fatigue syndrome: Objective measures of sleep

2004 Journal of Psychosomatic Research 56 (2); 207 – 212

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1542328110&partnerID=40>

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Purpose Chronic fatigue syndrome (CFS) is characterized by profound fatigue accompanied by disturbances of sleep, cognition, mood, and other symptoms. Our objective was to describe sleep architecture in CFS-discordant twin pairs. Methods We conducted a co-twin control study of 22 pairs of monozygotic twins where one twin met criteria for CFS and the co-twin was healthy. Twins underwent two nights of polysomnography. Results The percentage of Stage 3 and REM sleep was greater among the CFS twins than their healthy co-twins ($P < .05$ for both), but no other differences in sleep architecture including sleep latency, REM latency, and total sleep time were observed. Compared to their co-twins, CFS twins had higher values for the apnea-hypopnea index and apnea-hypopnea arousal index ($P < .05$ for both). Conclusion These results do not provide strong evidence for a major role for

abnormalities in sleep architecture in CFS. Respiration appears impaired in CFS, but these clinical abnormalities cannot alone account for the prominence of sleep complaints in this illness. The co-twin control methodology highlights the importance of selecting well-matched control subjects. © 2004 Elsevier Inc. All rights reserved.

Social and behavioural aspects

Vandenbergen J., Vanheule S., Rosseel Y., Desmet M., Verhaeghe P.

Unexplained chronic fatigue and core conflictual relationship themes: A study in a chronically fatigued population

2009 *Psychology and Psychotherapy: Theory, Research and Practice* 82 (1); 31 – 40

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65449176756&partnerID=40>

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Objective. Unexplained fatigue syndromes are multidimensional phenomena that involve a constellation of symptoms. This paper explores whether typical relationship patterns are associated with self-reported and clinically rated fatigue symptoms in chronically fatigued patients. **Method.** Relationship patterns were assessed by means of the core conflictual relationship theme (CCRT) method. This method examines transference patterns, and was applied to interview data collected from chronically fatigued patients (N = 30). Chronic fatigue was assessed by means of a self-report questionnaire and was also rated clinically. **Results.** Both self-reported and clinically rated fatigue correlated with relationship themes. The intensity of fatigue related to the perception of others as not respecting and as negatively interfering. The typical reaction of the self to relationships consists of feeling disrespected, anger, passivity, and reduced feelings of self-consistency. **Conclusion.** Patients' perception of interpersonal relationships as distressing may be pivotal in understanding these results. **Implications for clinical intervention and future research** are indicated. © 2009 The British Psychological Society.

Smith W.R., Strachan E.D., Buchwald D.

Coping, self-efficacy and psychiatric history in patients with both chronic widespread pain and chronic fatigue

2009 *General Hospital Psychiatry* 31 (4); 347 – 352

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67449083458&partnerID=40>

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Objective: To investigate the relationship of coping style and self-efficacy to functional impairment in a group of patients with both chronic widespread pain (CWP) and chronic fatigue, as well as the possible mediating role of psychiatric diagnosis. **Methods:** We identified 138 consecutive clinic patients who met criteria for CWP and chronic fatigue. We collected demographic and clinical characteristics, as well as measures of emotion-focused and problem-focused coping styles, fatigue-related self-efficacy and self-reported general health. Psychiatric diagnoses were determined with a structured interview. Short Form-36 subscales of pain-related and fatigue-related functioning were the dependent variables in ordinal multiple regression analyses to identify the best-fit model for each. **Results:** In the final model for pain, increased functional impairment was associated with increased emotion-focused coping as well as less education, lower general health scores and higher body mass index. Conversely, in the final model for fatigue, increased functional impairment was significantly associated with less emotion-focused coping, lower general health scores and lower self-efficacy. **Conclusions:** The unexpected finding that emotion-focused coping was associated differently with chronic pain and fatigue among patients who experience both symptoms is discussed in the context of the research on the effects of self-efficacy and possible treatment approaches. © 2009 Elsevier Inc. All rights reserved.

Christopher G., Thomas M.

Social problem solving in chronic fatigue syndrome: Preliminary findings

2009 Stress and Health 25 (2); 161 - 169

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650665031&partnerID=40>

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This paper investigates social problem solving in chronic fatigue syndrome (CFS), a condition characterized by reduced activity levels and excessive mental fatigue. Although intra- and interpersonal problems are prevalent, no studies have explored social problem-solving skills in this group. Patients were split into two groups: either high or low alexithymia, a condition associated with affect dysregulation. The high alexithymic group viewed problems as threatening, responding either impulsively or avoiding responding altogether; they were poor also in the use of compensatory strategies, which, taken together, increases the likelihood of a negative outcome from attempts at conflict resolution. These findings go some way in successfully identifying potential subgroupings in CFS sufferers and has important implications in terms of the therapy offered. Copyright © 2008 John Wiley & Sons, Ltd.

Wada K., Sakata Y., Theriault G., Aratake Y., Shimizu M., Tsutsumi A., Tanaka K., Aizawa Y.

Effort-reward imbalance and social support are associated with chronic fatigue among medical residents in Japan

2008 International Archives of Occupational and Environmental Health 81 (3); 331 – 336

<http://www.scopus.com/inward/record.url?eid=2-s2.0-36549018146&partnerID=40>

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The purpose of this study was to determine the associations of effort-reward imbalance and social support with chronic fatigue among medical residents in Japan. A total of 104 men and 42 women at 14 teaching hospitals participated in this study. Chronic fatigue was measured by the checklist individual strength questionnaire. Effort, reward and overcommitment were determined by the effort-reward questionnaire developed by Siegrist. Social support was determined by a visual analog scale. Sleeping hours for the last 30 days were estimated based on the number of overnight shifts worked, the average number of sleeping hours, and the number of hours of napping during overnight work. Multiple regression analysis was used to examine the multivariate relationship between these variables and chronic fatigue. In both men and women, effort-reward imbalance was positively associated, and higher social support was negatively associated with chronic fatigue. In men, higher overcommitment was positively associated with chronic fatigue. In women, longer sleeping hours was negatively associated with chronic fatigue and an interaction between sleeping hours and social support was found. The adjusted variance in fatigue explained by the exposure variables was 34% in men and 51% in women. The result of this study suggested that it is desirable to take these factors into consideration in the management of chronic fatigue among medical residents. © Springer-Verlag 2007.

Travers M.K., Lawler J.

Self within a climate of contention: Experiences of chronic fatigue syndrome

2008 Social Science and Medicine 66 (2); 315 – 326

<http://www.scopus.com/inward/record.url?eid=2-s2.0-36849046679&partnerID=40>

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Chronic fatigue syndrome (CFS) is a contested condition associated with scepticism and dispute. This qualitative project examines the illness experiences, and specifically the experiences of self, for people affected with CFS living in Australia. Using grounded theory methods, theory related to the process of self-renewal and adaptation associated with CFS is explicated. Narratives were derived from semi-structured interviews with 19 adults, including 3 people recovered from CFS. Analysis generated the narrative of the struggling self seeking renewal that defined the illness experience of CFS. The struggling self articulated the negative effects to self and personhood associated with CFS, defined as the violation of self, and the consequent efforts of participants to manage symptoms and decrease their violation by use of what was termed the Guardian Response and the Reconstructing Response. The Guardian Response provided protection and self-reclamation. The Reconstructing Response fostered self-renewal and meaning. The struggling self occurred within a climate of threats, and it was these threats which provided the catalyst for violation and the responses. Under different conditions the relative strengths of violation, guardianship or reconstruction fluctuated, and it was these fluctuations that presented the participants with the ongoing struggle of CFS. © 2007 Elsevier Ltd. All rights reserved.

Libman E., Creti L., Rizzo D., Jastremski M., Bailes S., Fichten C.S.

Descriptors of fatigue in chronic fatigue syndrome

2008 Journal of Chronic Fatigue Syndrome 14 (3); 37 – 45

<http://www.scopus.com/inward/record.url?eid=2-s2.0-39749148482&partnerID=40>

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Objective: To explore how individuals with chronic fatigue syndrome (CFS) describe their fatigue experience and examine how this differs from descriptions of fatigue in healthy controls. Methods: Fifty-two individuals with CFS and 27 controls listed words that described their fatigue. These words were grouped into 18 categories. Results: Individuals with CFS used more categories to describe their fatigue and more descriptors within each category. The most popular category used by both groups was energy depletion/physical weakness. CFS participants also experienced their fatigue as limiting their ability to function, frustrating, permanent/persistent, out of their control, depressing, and pervading all aspects of their lives. Controls reported that when they experienced fatigue, it was temporary, and they felt unmotivated, sleepy, and comfortable. Conclusion: The multidimensional descriptive pattern characterizing the fatigue of individuals with CFS differs dramatically from the experienced fatigue of healthy individuals, suggesting their "language of fatigue" has a distinctive quality. Copyright © by The Haworth Press, Inc. All rights reserved.

Dickson A., Knussen C., Flowers P.

'That was my old life; It's almost like a past-life now': Identity crisis, loss and adjustment amongst people living with Chronic Fatigue Syndrome

2008 *Psychology and Health* 23 (4); 459 - 476

<http://www.scopus.com/inward/record.url?eid=2-s2.0-42049105957&partnerID=40>

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Individual in-depth interviews were conducted with 14 people with Chronic Fatigue Syndrome (CFS). The interviews centred on the experience of living with the condition from the participants' own perspectives. All interviews were transcribed verbatim and were analysed using Interpretative Phenomenological Analysis. Three inter-related themes were presented: 'Identity crisis: agency and embodiment'; 'Scepticism and the self' and 'Acceptance, adjustment and coping'. Participants reported an ongoing sense of personal loss characterised by diminishing personal control and agency. An inability to plan for the future and subsequent feelings of failure, worthlessness and insignificance ensued. Scepticism in the wider social environment only heightened the consequential identity crisis. The importance of acceptance for adjusting to a life with CFS was highlighted. The findings are discussed in relation to extant literature and issues for health psychology are raised.

Cho H.J., Menezes P.R., Bhugra D., Wessely S.

The awareness of chronic fatigue syndrome: A comparative study in Brazil and the United Kingdom

2008 *Journal of Psychosomatic Research* 64 (4); 351 – 355

<http://www.scopus.com/inward/record.url?eid=2-s2.0-41249086467&partnerID=40>

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Objective: While in many Western affluent countries there is widespread awareness of chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), little is known about the awareness of CFS/ME in low- and middle-income countries. We compared the awareness of CFS in Brazil and the United Kingdom. Methods: Recognition and knowledge of CFS were assessed among 120 Brazilian specialist doctors in two major university hospitals using a typical case vignette of CFS. We also surveyed 3914 and 2435 consecutive attenders in Brazilian and British primary care clinics, respectively, concerning their awareness of CFS. Results: When given a typical case vignette of CFS, only 30.8% [95% confidence interval (CI), 22.7-39.9%] of Brazilian specialist doctors mentioned chronic fatigue or CFS as a possible diagnosis, a proportion substantially lower than that observed in Western affluent countries. Similarly, only 16.2% (95% CI, 15.1-17.4%) of Brazilian primary care attenders were aware of CFS, in contrast to 55.1% (95% CI, 53.1-57.1%) of their British counterparts ($P < .001$). This difference remained highly significant after controlling for patients' sociodemographic and socioeconomic characteristics ($P < .001$). Conclusions: The awareness of CFS was substantially lower in Brazil than the United Kingdom. The observed difference may influence patients' help-seeking behavior and both doctors' and patients' beliefs and attitudes in relation to fatigue-related syndromes. Attempts to promote the awareness of CFS should be considered in Brazil, but careful plans are required to ensure the delivery of sound evidence-based information. © 2008 Elsevier Inc. All rights reserved.

Cho H.J., Bhugra D., Wessely S.

'Physical or psychological?' - A comparative study of causal attribution for chronic fatigue in Brazilian and British primary care patients

2008 *Acta Psychiatrica Scandinavica* 118 (1); 34 – 41

<http://www.scopus.com/inward/record.url?eid=2-s2.0-45149108577&partnerID=40>

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Objective: Causal attribution influences symptom experience, help-seeking behaviour and prognosis in chronic fatigue syndrome. We compared causal attribution of patients with unexplained chronic fatigue (UCF) in Brazil and Britain. **Method:** Primary care attenders in São Paulo (n = 3914) and London (n = 2459) were screened for the presence of UCF. Those with UCF (São Paulo n = 452; London n = 178) were assessed for causal attribution (physical vs. psychosocial), perceived chronicity (i.e. reported duration of fatigue) and disability. **Results:** British UCF patients were more likely to attribute their fatigue to physical causes (adjusted odds ratio 1.70, P = 0.037) and perceived their fatigue to be more chronic (adjusted beta 0.15, P = 0.002). There was no significant difference in current disability (adjusted beta -0.01, P = 0.81). **Conclusion:** Despite similar disability levels, UCF patients in different cultural settings presented different attributions and perceptions about their illness. Sociocultural factors may have an important role in shaping illness attribution and perception around chronic fatigue. Copyright © 2008 The Authors.

Arroll M.A., Senior V.

Individuals' experience of chronic fatigue syndrome/myalgic encephalomyelitis: An interpretative phenomenological analysis

2008 *Psychology and Health* 23 (4); 443 - 458

<http://www.scopus.com/inward/record.url?eid=2-s2.0-42049090772&partnerID=40>

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Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a condition of unknown aetiology that consists of symptoms such as fatigue, muscle and joint pain, gastric problems and a range of neurological disturbances. Due to the fact that these symptoms are complaints that most individuals will experience to a varying degree, it seems pertinent to investigate the processes by which those with CFS/ME conceptualise their symptoms and the experience of reaching a diagnosis. Participants were recruited from local CFS/ME support groups. Eight semi-structured telephone interviews were conducted and transcribed, and the verbatim transcriptions were analysed according to interpretative phenomenological analysis (IPA). Six distinct themes were uncovered that illustrated the participants' experience and perception of their symptoms. These included symptomatology and illness course, interference with daily and working life, frequency of symptoms, external information, diagnosis and treatment. The findings were discussed in terms of internal and external cues related to symptom perception and the discovery that the possession of a diagnosis did not necessarily signify the end of the journey.

Wolbeek M., Van Doornen L.J.P., Kavelaars A., Heijnen C.J.
Predictors of persistent and new-onset fatigue in adolescent girls

2008 Pediatrics 121;3

<http://www.scopus.com/inward/record.url?eid=2-s2.0-40949110624&partnerID=40>

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OBJECTIVE. The purpose of this study was to investigate the stability of fatigue in adolescents and to explore whether psychological, somatic, and lifestyle factors are involved in the onset and persistence of fatigue during adolescence. **METHODS.** In this longitudinal study, a total of 653 adolescent girls (aged 14.40 \pm 1.45 years) who previously participated in an epidemiological study filled out questionnaires 6 (T2) and 12 (T3) months after the initial assessment (T1). Fatigue severity, depression, anxiety, and chronic fatigue syndrome-related symptoms were assessed. We determined the prevalence of severely fatigued cases at T2 and T3 and evaluated whether persistently fatigued participants initially differed from nonfatigued participants and participants with transient fatigue. We examined which factors predicted the development of new-onset fatigue and investigated whether changes in fatigue covaried with changes in other complaints and changes in lifestyle. **RESULTS.** Of all participants who were severely fatigued at T1, 25.7% were persistently fatigued throughout the study. Persistently fatigued participants had higher levels of depression and anxiety at the beginning of the study, were less physically active, and slept shorter. New-onset fatigue was predicted by depression, less physical activity, and more nightlife activities. Interestingly, new onset was not predicted by initial levels of fatigue. Persistently fatigued participants did not differ in initial fatigue severity from short-term fatigued patients. A decrease in fatigue severity was associated with a decrease in depression, anxiety, and chronic fatigue syndrome-related symptoms and, to a lesser extent, with an increase in physical activity and sleep duration. **CONCLUSIONS.** The stability of severe fatigue among adolescents is substantial. The involvement in the onset and persistence of fatigue suggests that both preventive and therapeutic strategies with respect to fatigue treatment in adolescents should concentrate on emotional well-being. Moreover, adolescents at risk should be stimulated to spend more time on physical activities and to sleep longer. Copyright © 2008 by the American Academy of Pediatrics.

Jorgensen R.
Chronic fatigue: An evolutionary concept analysis

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-54449083199&partnerID=40>

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Aim. This paper is a report of a concept analysis of chronic fatigue. **Background.** Fatigue is a prevalent symptom encompassing both acute and chronic manifestations. It is chronic fatigue that is most problematic because of its duration and impact on life quality. The rise in prevalence of chronic conditions will result in a need to address coexistent symptoms, clarification of which is needed. Chronic fatigue is one of the most common symptoms in chronic illness. Clarification of the concept and an understanding of its use by discipline are needed. **Data sources.** The evolutionary method of concept analysis was used to ascertain the attributes, antecedents, consequences and surrogate terms for chronic fatigue. A review of the literature published between 1966 and 2007 was carried out to determine the contextual use of the concept of chronic fatigue among disciplines. Sources used for this analysis included CINAHL, Medline, PsychINFO and Social Work Abstracts and the search yielded 66 papers. **Results.** The chronic fatigue experience is associated with a multitude of physical, psychological and social factors. The defining attributes of chronic fatigue are constancy, abnormality, whole-body experience, inexplicability and disabling. The antecedents of chronic fatigue are physical disease, psychopathology, female gender and a history of abuse. Consequences found include social isolation

and stigmatization, physical inactivity, psychological disturbances and a reduced quality of life. Conclusion. Further research is needed to identify the aetiology of chronic fatigue and to address the social context of living with this disabling symptom. © 2008 Blackwell Publishing Ltd.

Jhanji V., Beltz J., Vajpayee R.B.

Contact lens-related acanthamoeba keratitis in a patient with chronic fatigue syndrome.

2008 Eye & contact lens 34 (6); 335 – 336

<http://www.scopus.com/inward/record.url?eid=2-s2.0-58149296519&partnerID=40>

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PURPOSE: To report a case of contact lens-related Acanthamoeba keratitis associated with improper lens hygiene in a patient with chronic fatigue syndrome (CFS). **METHODS:** Contact lens-related Acanthamoeba keratitis was diagnosed in a 58-year-old man with a history of CFS. After medical management failed to prevail, a penetrating keratoplasty was performed in the affected eye. **RESULTS:** There was no recurrence of Acanthamoeba keratitis after surgery. Complete re-epithelialization of the graft was observed with a best-corrected visual acuity of 20/80 in the operated eye at the last follow-up (3 months). **CONCLUSIONS:** Our case report highlights the fact that concurrent incapacitating illnesses like CFS may not allow proper care of contact lenses thereby making patients prone to contact lens-related corneal infections.

Baetz M., Bowen R.

Chronic pain and fatigue: Associations with religion and spirituality.

2008 Pain research & management : the journal of the Canadian Pain 13 (5); 383 – 388

<http://www.scopus.com/inward/record.url?eid=2-s2.0-61949429855&partnerID=40>

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ACKGROUND: Conditions with chronic, non-life-threatening pain and fatigue remain a challenge to treat, and are associated with high health care use. Understanding psychological and psychosocial contributing and coping factors, and working with patients to modify them, is one goal of management. An individual's spirituality and/or religion may be one such factor that can influence the experience of chronic pain or fatigue. **METHODS:** The Canadian Community Health Survey (2002) obtained data from 37,000 individuals 15 years of age or older. From these data, four conditions with chronic pain and fatigue were analyzed together -- fibromyalgia, back pain, migraine headaches and chronic fatigue syndrome. Additional data from the survey were used to determine how religion and spirituality affect psychological well-being, as well as the use of various coping methods. **RESULTS:** Religious persons were less likely to have chronic pain and fatigue, while those who were spiritual but not affiliated with regular worship attendance were more likely to have those conditions. Individuals with chronic pain and fatigue were more likely to use prayer and seek spiritual support as a coping method than the general population. Furthermore, chronic pain and fatigue sufferers who were both religious and spiritual were more likely to have better psychological well-being and use positive coping strategies. **INTERPRETATION:** Consideration of an individual's spirituality and/or religion, and how it may be used in coping may be an additional component to the overall management of chronic pain and fatigue.

Vervoort T., Crombez G., Buysse A., Goubert L., Backer T.D., Ickes W.

Brief report: The accuracy of parents for the thoughts and feelings of their adolescent suffering from chronic fatigue: A preliminary study of empathy

2007 Journal of Pediatric Psychology 32 (4); 494 – 499

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34347222536&partnerID=40>

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Objective: This study examined the actual and estimated empathic accuracy (EA) of the parents of adolescents with chronic fatigue syndrome (CFS). Methods: The actual EA of both parents (n = 24) was assessed in relation to the thoughts and feelings of their child (n = 14) about CFS and about other life events. Adolescents were also asked to estimate the parents' EA. Results: For the actual EA, both parents were significantly less accurate regarding the adolescent's thoughts and feelings about CFS than about other life events. Fathers were just as empathically accurate as mothers. For the estimated EA, however, results indicated that adolescents perceived their mother to be more empathically accurate than their father. Actual EA and estimated EA about CFS were negatively correlated for fathers, not for mothers. Conclusions: Results are discussed in terms of the importance of assessing EA in relation to other dimensions of empathic understanding and distress in the observer. © The Author 2006. Published by Oxford University Press on behalf of the Society of Pediatric Psychology. All rights reserved.

Horton-Salway M.

The 'ME Bandwagon' and other labels: Constructing the genuine case in talk about a controversial illness

2007 British Journal of Social Psychology 46 (4); 895 – 914

<http://www.scopus.com/inward/record.url?eid=2-s2.0-38149003763&partnerID=40>

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This paper examines the discourse of morality surrounding 'ME' as a contested illness, looking at how GPs and ME group members differentiate between the category of 'genuine ME sufferer' and the 'bandwagon'. 'Jumping on the bandwagon' is a metaphor commonly used to describe the activity of 'following the crowd' in order to gain an advantage. This discursive analysis shows how 'bandwagon' categories are constructed in contrast to the category of genuine sufferer. People who jump on the bandwagon are accused of matching their symptoms to media stereotypes, adopting trendy illnesses ('fads',) or using 'tickets' to avoid facing up to psychological illnesses. Both GPs and ME group members construct a differential moral ordering of physical and psychological illness categories, where the latter assumes a lesser status. The paper concludes that against a background of medical uncertainty and controversy, the 'bandwagon' and other derogatory labels function as contrast categories that work to establish the existence of 'ME' as a genuine illness. © 2007 The British Psychological Society.

Gray S.E., Rutter D.R.

Illness representations in young people with Chronic Fatigue Syndrome

2007 *Psychology and Health* 22 (2); 159 - 174

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847031718&partnerID=40>

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Leventhal's commonsense model of self-regulation has attracted a great deal of research in recent years, but its possible implications for understanding young people with chronic illness have received little attention. The purpose of this study is to examine children and young people with chronic fatigue syndrome (CFS) and to explore (a) the characteristics of their illness representations, (b) whether those representations are associated with their physical functioning and perceived quality of life and (c) whether coping strategies may act as mediators between representations and those outcomes. A total of 85 participants, ranging in age from 8 to 25 years, were recruited from the website of a self-help group for young people with CFS. They were asked to complete three questionnaires, measuring illness representations, coping strategies, and physical functioning and quality of life. The results showed that illness representations formed characteristic patterns, that they were associated with both physical functioning and quality of life, and that coping partially mediated the relationship between illness representations and outcome. We conclude that young people's representations of their CFS play an important role in coping and outcome. The implications of the findings are discussed for both theory and clinical practice, and suggestions are made for further research. © 2007 Taylor & Francis.

Edwards C.R., Thompson A.R., Blair A.

An 'overwhelming illness': Women's experiences of learning to live with chronic fatigue syndrome/myalgic encephalomyelitis

2007 *Journal of Health Psychology* 12 (2); 203 – 214

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33846695113&partnerID=40>

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The processes through which people learn to live with CFS/ME are poorly understood and have not been rigorously explored within the literature. Semi-structured interviews were conducted with eight women and analysed using interpretative phenomenological analysis. Participants initially described being 'overwhelmed' by CFS/ME. Attempts at seeking help were unsatisfactory and participants described feeling let down and disbelieved. Participants reacted to this by identifying types of 'self-help' and assertively taking more responsibility for their illness and its treatment. Acquiring social support and greater knowledge were key mediating factors in the emergence of control and acceptance. The relevance of the themes to existing research and the implications for clinical practice are considered. Copyright © 2007 SAGE Publications.

Dickson A., Knussen C., Flowers P.

Stigma and the delegitimation experience: An interpretative phenomenological analysis of people living with chronic fatigue syndrome

2007 *Psychology and Health* 22 (7); 851 - 867

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34547684263&partnerID=40>

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Individual in-depth interviews with 14 people with chronic fatigue syndrome (CFS) were conducted, focusing on the experience of living with CFS. The interviews were transcribed verbatim and were

analysed for recurrent themes using interpretative phenomenological analysis (IPA). Here we present two inter-related themes: "Negotiating a diagnosis" and "Negotiating CFS with loved ones". Participants reported delay, negotiation and debate over diagnosis: further, they perceived their GPs to be sceptical, disrespectful and to be lacking in knowledge and interpersonal skills. However, participants found delegitimising encounters with their partners more difficult to deal with. Participants viewed such delegitimation as a form of personal rejection; they were hurt by their loved ones' reactions and subsequently pondered the price of love, respect and friendship. The findings are discussed in relation to extant literature, and recommendations for future research are suggested.

Crofford L.J.

Violence, stress, and somatic syndromes

2007 Trauma, Violence, and Abuse 8 (3); 299 – 313

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34250787560&partnerID=40>

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Syndromes characterized by pain, fatigue, mood disorder, cognitive dysfunction, and sleep disturbance have been referred to as stress-related somatic disorders by virtue of the observation that onset and exacerbation of symptoms occur with stress. These syndromes include but are not limited to fibromyalgia, chronic fatigue syndrome, temporomandibular disorder, and irritable bowel syndrome. As with most chronic illnesses, genetic susceptibility and lifetime environmental exposures play a role in creating vulnerability to disease. Cumulative lifetime stress has been associated with a number of physiologic changes in the brain and body that reflect dysregulated hormonal and autonomic activity. Exposure to the stressor of violence is likely to create a state of vulnerability for the stress-related somatic syndromes and also to contribute to symptom expression and severity. Understanding the relationship between violence, stress, and somatic syndromes will help in clarifying the consequences of violence exposure to long-term health and health-related quality of life. © Sage Publications, Inc. 2007.

Schur E.A., Noonan C., Smith W.R., Goldberg J., Buchwald D.

Body mass index and fatigue severity in chronic fatigue syndrome

2007 Journal of Chronic Fatigue Syndrome 14 (1); 69 – 77

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34249302413&partnerID=40>

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Background: It is uncertain how much fatigue is related to weight in patients with chronic fatigue syndrome (CFS). Objective: To assess the association of body mass index (BMI) and fatigue in CFS patients. Methods: Consecutive patients seen in a referral-based specialty clinic were eligible if they met CFS criteria and had completed required measures. Fatigue measures were the vitality subscale of the Medical Outcomes Short-Form 36 and the global fatigue index from the Multidimensional Assessment of Fatigue. Results: In women, there was no relationship between BMI and vitality subscale or global fatigue index scores ($P = 0.99$ and $P = 0.44$). For men, vitality subscale scores significantly decreased as BMI increased ($P = 0.02$). Conclusions: In CFS patients, the prevalence of obesity was low despite risk factors for weight gain. Fatigue severity and BMI were unrelated in women with CFS, but this relationship may differ for men. Copyright © by The Haworth Press, Inc. All rights reserved.

Guise J., Widdicombe S., McKinlay A.

'What is it like to have ME?': The discursive construction of ME in computer-mediated communication and face-to-face interaction

2007 Health 11 (1); 87 - 108

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33845329924&partnerID=40>

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ME (Myalgic Encephalomyelitis) or CFS (chronic fatigue syndrome) is a debilitating illness for which no cause or medical tests have been identified. Debates over its nature have generated interest from qualitative researchers. However, participants are difficult to recruit because of the nature of their condition. Therefore, this study explores the utility of the internet as a means of eliciting accounts. We analyse data from focus groups and the internet in order to ascertain the extent to which previous research findings apply to the internet domain. Interviews were conducted among 49 members of internet groups (38 chatline, 11 personal) and 7 members of two face-to-face support groups. Discourse analysis of descriptions and accounts of ME or CFS revealed similar devices and interactional concerns in both internet and face-to-face communication. Participants constructed their condition as serious, enigmatic and not psychological. These functioned to deflect problematic assumptions about ME or CFS and to manage their accountability for the illness and its effects.

Whitehead L.C.

Quest, chaos and restitution: Living with chronic fatigue syndrome/myalgic encephalomyelitis

2006 Social Science and Medicine 62 (9); 2236 – 2245

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33644908770&partnerID=40>

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Chronic illness is disruptive, threatening people's sense of identity and taken for granted assumptions. Transformations in values, expectations and life priorities are likely to be experienced and in order to regain a coherent sense of self, people must interpret their experiences. People with difficult to diagnose illnesses can find themselves living with greater uncertainty and stigma. This paper explores how people with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) describe and interpret their illness experience by applying Arthur Frank's narrative typologies to analyse interviews with 17 British people with CFS/ME. The analysis proposes that a trajectory of narrative typologies is experienced, starting with a restitution narrative, moving to a chaos narrative and, for most, back to a restitution narrative and on to a quest narrative. The presentation of narrative types put forward by people living with CFS/ME differ to those presented by people who are HIV positive and have been treated for breast cancer. © 2005 Elsevier Ltd. All rights reserved.

Whitehead L.

Toward a trajectory of identity reconstruction in chronic fatigue syndrome/myalgic encephalomyelitis: A longitudinal qualitative study

2006 International Journal of Nursing Studies 43 (8); 1023 – 1031

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33749437868&partnerID=40>

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Background: Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is an illness associated with high levels of physical and cognitive disability over a prolonged period of time. Recovery from CFS/ME can be interspersed with relapses. Further, the legitimacy of the illness continues to be questioned within and beyond the health profession. Aim: This paper examines the reconstruction of self-identity for those experiencing CFS/ME. Method: This longitudinal qualitative study involved up to three in-depth interviews with 17 people with CFS/ME and family members. Results: A trajectory that

describes transitions in identity over time and the range of elements that influence these is proposed. During the acute phase of illness, characterised by total debility, people adopted the traditional sick role. The medium term phase highlighted movement between disability as part of the total self, total debility, and/or the adoption of a supernormal identity. The longer-term phase was defined for the majority of participants as the positive reconstruction of self. Identity was contingent with positive and negative experiences and responses co-existing with the potential to 'tip' the balance and perceived identity. In the longer term people's identity became more static with the development of coping strategies to maintain this. The trajectory can be described as pendular and movement between each type of identity was possible during all phases of the illness experience depending on the nature and impact of the illness and responses given to these. The proposed trajectory represents a dynamic model of identity reconstruction. Conclusion: Understanding the patients' experience and recognising that different stages may exist is important for health professionals. This awareness can enhance shared understanding and opportunities to work with people in negotiating the impact of illness. © 2006 Elsevier Ltd. All rights reserved.

Van Hoof E., De Becker P., De Meirleir K.

Pediatric chronic fatigue syndrome and Munchausen-by-proxy: A case study

2006 Journal of Chronic Fatigue Syndrome 13 (02-Mar); 45 – 53

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847371597&partnerID=40>

Department of Human Physiology (MFYS), Faculty of Human Exercise and Human Education, and Cognitive and Biological Psychology, Vrije Universiteit Brussel (VUB), Belgium; University of Hasselt, Belgium; Department of Human Physiology (MFYS), Faculty of Human Exercise and Human Education, Vrije Universiteit Brussel (VUB), Belgium; Universiteit Hasselt, Faculty of Medicine, Department of Behavioral Sciences, Agoralaan-Gebound, 3590 Diepenbeek, Belgium

Pediatric chronic fatigue syndrome (CFS) posits even more challenges for professional caregivers in comparison with adult CFS samples. Most children with CFS display a decrease in school attendance and a decrease in social activities. As several conditions such as school phobia, primary psychiatric disorders or family disturbance present the same characteristics, the diagnostic process appears more complex. Family disturbance, moreover, is often specified as child abuse, neglect or even Munchausen-by-proxy. As skepticism is frequently associated with a diagnosis of CFS, patients and parents must fend for themselves, fighting allegations of child abuse and neglect. This case study illustrates what happens when such allegations are put forward. © 2006 by The Haworth Press, Inc. All rights reserved.

Van Damme S., Crombez G., Van Houdenhove B., Mariman A., Michielsen W.

Well-being in patients with chronic fatigue syndrome: The role of acceptance

2006 Journal of Psychosomatic Research 61 (5); 595 – 599

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33750459889&partnerID=40>

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Objective: Research in chronic pain patients has shown that accepting the chronic nature of their illness is positively related to quality of life. The aim of this study was to investigate whether acceptance is also associated with better well-being in patients suffering from chronic fatigue syndrome (CFS). Methods: Ninety-seven patients completed a battery of questionnaires measuring fatigue, functional impairment, psychological distress, and acceptance. Results: Results indicated that acceptance has a positive effect upon fatigue and psychological aspects of well-being. More specifically, acceptance was related to more emotional stability and less psychological distress, beyond the effects of demographic variables, and fatigue severity. Conclusion: We suggest that promoting acceptance in patients with CFS may often be more beneficial than trying to control largely uncontrollable symptoms. © 2006 Elsevier Inc. All rights reserved.

Torres-Harding S.R., Jordan K., Jason L.A., Arias R.
Psychosocial and physical impact of chronic fatigue in a community-based sample of children and adolescents

2006 Journal of Chronic Fatigue Syndrome 13 (02-Mar); 55 – 74

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847375083&partnerID=40>

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Background: Few studies have examined the problem of chronic fatigue in children and adolescents and its potential impact on functioning. Chronic fatigue may have a negative impact on school functioning, family activities, psychological well-being, physical functioning, and severity of medical symptomatology. Objectives: This study compared psychosocial, family, and physical functioning between a randomly selected community based sample of 36 children and adolescents with chronic fatigue and a group of 21 children and adolescents without fatigue. Methods: Children and parents completed a comprehensive medical history questionnaire and questionnaires assessing psychological functioning, family functioning, and school attendance. Results: Results indicated that children with chronic fatigue tended to have more difficulties in overall physical and psychological functioning, as measured by the Child Health Questionnaire and the Child Behavior Checklist. In addition, children in the chronic fatigue group experienced disruptions in a range of activities and reported more severe physical symptomatology when compared to children without fatigue. Conclusions: Findings suggest that children and adolescents with chronic fatigue may have a range of associated difficulties, including limitations in physical and psychosocial functioning and a negative impact on the ability to engage in normative activities. © 2006 by The Haworth Press, Inc. All rights reserved.

Taylor R.R., Kulkarni S., Shiraishi Y.
Conservation of resources and quality of life in individuals with chronic fatigue syndrome

2006 Journal of Chronic Fatigue Syndrome 13 (4); 5 – 15

<http://www.scopus.com/inward/record.url?eid=2-s2.0-35948953201&partnerID=40>

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Objective: To examine the relationship between resources and quality of life in individuals with chronic fatigue syndrome (CFS). Participants and Study Design: A cross-sectional design was used to describe associations between resource loss and gain and quality of life for 47 individuals diagnosed with CFS. Main Outcome Measures: The Conservation of Resources Evaluation was used to measure resources in terms of perceived loss and gain. Health-related quality of life was assessed with the Quality of Life Index. Results: Total resource loss and total resource gain were significant correlates of overall quality of life. Gains in self-esteem, energy, and work resources were associated with higher-perceived quality of life. Material loss and energy loss were associated with lower-perceived quality of life. Conclusions: Findings for the relationships between perceived resources of self-esteem, work, material items, and energy and perceived quality of life can be used inform future rehabilitation efforts. These relationships appear to occur independently of illness severity among individuals CFS. © Copyright by The Haworth Press, Inc. All rights reserved.

Swoboda D.A.

The social construction of contested illness legitimacy: A grounded theory analysis

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-33846315810&partnerID=40>

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This study examines the social influences that shape how individuals come to believe they have a contested illness and the explanations of illness legitimacy that result. Chronic fatigue syndrome, multiple chemical sensitivities, and Gulf War syndrome have all been identified as contested illnesses because their etiology, diagnosis, and prevalence are controversial. Narratives from in-depth interviews with 22 individuals who identified themselves as having these illnesses were analysed using a grounded theory approach. Findings indicate that claiming medical legitimacy for a contested illness involves a difficult and protracted process in which sufferers develop social representations of the etiology, diagnostic criteria, trajectory, and treatment of their illnesses. Study results shed light on the role of sufferers in the social construction of the medical and cultural legitimacy of emerging illnesses. © 2006 SAGE Publications.

Nater U.M., Wagner D., Solomon L., Jones J.F., Unger E.R., Papanicolaou D.A., Reeves W.C., Heim C.
Coping styles in people with chronic fatigue syndrome identified from the general population of Wichita, KS

2006 *Journal of Psychosomatic Research* 60 (6); 567 – 573

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646758218&partnerID=40>

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Objective: Studies of primary and tertiary care patients suggest that maladaptive coping styles contribute to the pathogenesis and maintenance of chronic fatigue syndrome (CFS). We assessed coping styles in persons with unexplained fatigue and nonfatigued controls in a population-based study. Methods: We enrolled 43 subjects meeting the 1994 Research Case Definition of CFS, matching them with 61 subjects with chronic unexplained fatigue who did not meet criteria for CFS [we term them insufficient symptoms or fatigue (ISF)] and 60 non-ill (NI) controls. Coping styles and clinical features of CFS were assessed using standard rating scales. Results: Subjects with CFS and ISF reported significantly more escape-avoiding behavior than NI controls. There were no differences between the CFS and ISF subjects. Among participants with CFS, escape-avoiding behavior was associated with fatigue severity, pain, and disability. Conclusions: We demonstrate significantly higher reporting of maladaptive coping in a population-based sample of people with CFS and other unexplained fatiguing illnesses defined by reproducible standardized clinical empirical means in comparison to NI controls. © 2006 Elsevier Inc. All rights reserved.

Huibers M.J.H., Leone S.S., Kant I.J., Knottnerus J.A.

Chronic fatigue syndrome-like caseness as a predictor of work status in fatigued employees on sick leave: Four year follow up study

2006 Occupational and Environmental Medicine 63 (8); 570 – 572

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33746503094&partnerID=40>

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Objective: To assess whether CFS-like caseness (meeting the criteria for chronic fatigue syndrome (CFS)) predicts work status in the long term. Methods: Prospective study in a sample of fatigued employees absent from work. Data were collected at baseline and four years later, and included CFS-like caseness and work status (inactive work status and full work incapacity). Results: CFS-like cases at baseline were three times more likely to be unable to work at follow up than fatigued employees who did not meet CFS criteria at baseline (ORs 3-3.3). These associations grew even stronger when demographic and clinical confounders were controlled for (ORs 3.4-4.4). Conclusion: A CFS-like status (compared to non-CFS fatigue) proved to be a strong predictor of an inactive work status and full work incapacity in the long term. Since little is known about effective interventions that prevent absenteeism and work incapacity or facilitate return to work in subjects with chronic fatigue, there is a great need for powerful early interventions that restore or preserve the ability to work, especially for workers who meet criteria for CFS.

Heim C., Wagner D., Maloney E., Papanicolaou D.A., Solomon L., Jones J.F., Unger E.R., Reeves W.C.

Early adverse experience and risk for chronic fatigue syndrome: Results from a population-based study

2006 Archives of General Psychiatry 63 (11); 1258 – 1266

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Context: Chronic fatigue syndrome (CFS) is an important public health problem. The causes of CFS are unknown and effective prevention strategies remain elusive. A growing literature suggests that early adverse experience increases the risk for a range of negative health outcomes, including fatiguing illnesses. Identification of developmental risk factors for CFS is critical to inform pathophysiological research and devise targets for primary prevention. Objective: To examine the relationship between early adverse experience and risk for CFS in a population-based sample of clinically confirmed CFS cases and nonfatigued control subjects. Design, Setting, and Participants: A case-control study of 43 cases with current CFS and 60 nonfatigued controls identified from a general population sample of 56 146 adult residents from Wichita, Kan. Main Outcome Measures: Self-reported childhood trauma (sexual, physical, and emotional abuse and emotional and physical neglect) and psychopathology (depression, anxiety, and posttraumatic stress disorder) by CFS status. Results: The CFS cases reported significantly higher levels of childhood trauma and psychopathology compared with the controls. Exposure to childhood trauma was associated with a 3- to 8-fold increased risk for CFS across different trauma types. There was a graded relationship between the degree of trauma exposure and CFS risk. Childhood trauma was associated with greater CFS symptom severity and with symptoms of depression, anxiety, and posttraumatic stress disorder. The risk for CFS conveyed by childhood trauma increased with the presence of concurrent psychopathology. Conclusions: This study provides evidence of increased levels of multiple types of childhood trauma in a population-based sample of clinically confirmed CFS cases compared with nonfatigued controls. Our results suggest that childhood trauma is

an important risk factor for CFS. This risk was in part associated with altered emotional state. Studies scrutinizing the psychological and neurobiological mechanisms that translate childhood adversity into CFS risk may provide direct targets for the early prevention of CFS. ©2006 American Medical Association. All rights reserved.

Dumit J.

Illnesses you have to fight to get: Facts as forces in uncertain, emergent illnesses

2006 Social Science and Medicine 62 (3); 577 – 590

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Chronic fatigue syndrome and multiple chemical sensitivity are two clusters of illnesses that are pervaded by medical, social and political uncertainty. This article examines how facts are talked about and experienced in struggles over these emergent, contested illnesses in the US. Based principally on a large archive of internet newsgroup postings, and also on fieldwork and on published debates, it finds that (1) sufferers describe their experiences of being denied healthcare and legitimacy through bureaucratic categories of exclusion as dependent upon their lack of biological facts; (2) institutions manage these exclusions rhetorically through exploiting the open-endedness of science to deny efficacy to new facts; (3) collective patient action responds by archiving the systematic nature of these exclusions and developing counter-tactics. The result is the maintenance of these very expensive struggles for all involved. © 2005 Elsevier Ltd. All rights reserved.

Richards J., Chaplin R., Starkey C., Turk J.

Illness beliefs in chronic fatigue syndrome: A study involving affected adolescents and their parents

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Background: The aim of the study was to investigate the beliefs of young people with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) and their parents, about illness causes and management. Method: Twenty-one young people with CFS/ME and their parents participated in an open-ended interview. Results: Infective causes were identified by the majority of respondents, and psychological ones by a minority. Many highlighted reducing activity and resting in symptom management. Positive and negative experiences of psychiatric and psychological treatments were recorded. Conclusion: Professionals should carefully explore the illness related beliefs of young people with CFS/ME and parental beliefs in order to agree treatment plans. © 2006 Association for Child and Adolescent Mental Health.

Van De Putte E.M., Engelbert R.H.H., Kuis W., Sinnema G., Kimpen J.L.L., Uiterwaal C.S.P.M.
Chronic fatigue syndrome and health control in adolescents and parents

2005 Archives of Disease in Childhood 90 (10); 1020 – 1024

<http://www.scopus.com/inward/record.url?eid=2-s2.0-26044476967&partnerID=40>

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Aims: To explore the locus of health control in adolescents with chronic fatigue syndrome (CFS) and their parents in comparison with healthy adolescents and their parents. **Methods:** In this cross-sectional study 32 adolescents with CFS were compared with 167 healthy controls and their respective parents. The Multidimensional Health Locus of Control (MHLC) questionnaire was applied to all participants. **Results:** There was significantly less internal health control in adolescents with CFS than in healthy controls. An increase of internal health control of one standard deviation was associated with a 61% reduced risk for CFS (OR = 0.39, 95% CI 0.25 to 0.61). Internal health control of the parents was also protective (OR fathers: 0.57 (95% CI 0.38 to 0.87); OR mothers: 0.74 (95% CI 0.50 to 1.09)). The external loci of health control were higher in adolescents with CFS and in their parents. Increased levels of fatigue (56%) were found in the mothers of the adolescents with CFS, in contrast with the fathers who reported a normal percentage of 13. **Conclusions:** In comparison with healthy adolescents, adolescents with CFS and their parents show less internal health control. They attribute their health more to external factors, such as chance and physicians. This outcome is of relevance for treatment strategies such as cognitive behaviour therapy, for which health behaviour is the main focus.

Taylor R.R.

Can the social model explain all of disability experience? Perspectives of persons with chronic fatigue syndrome

2005 American Journal of Occupational Therapy 59 (5); 497 – 506

<http://www.scopus.com/inward/record.url?eid=2-s2.0-27744596114&partnerID=40>

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OBJECTIVE. The social model of disability has had a major influence on the academic field of disability studies and on contemporary understandings of the causes and experience of disability. The purpose of this study was to examine the adequacy of the social model for explaining the disability experience of persons with chronic fatigue syndrome (CFS). **METHODS.** This qualitative study examined the experiences of 47 adults with CFS participating in a research project that aimed to evaluate a participant-designed rehabilitation program. Data were aggregated from focus group interviews, open-ended questionnaires, progress notes, and from a program evaluation questionnaire. Data analysis was based on a grounded theory approach and used triangulation of multiple data sources and member checks to assure dependability of findings. **RESULTS.** Four themes emerged from the analysis: (1) minimization and mistrust of the disability; (2) negative experiences of impairment; (3) lack of identification with the disability community; and (4) the focus on advocacy as a quest for legitimacy. These themes varied in the extent to which they conformed to the principles set forth by the social model. **CONCLUSIONS.** Although the social model has important contributions to lend to occupational therapy practice, it is important to recognize that it may not capture the full reality of disability. In particular, the social model has serious limitations in describing the disability experience of individuals with disabilities who do not have visibly obvious disabilities and whose impairments do not conform to the traditional viewpoint of disability.

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Why did I get chronic fatigue syndrome? A qualitative interview study of causal attributions in women patients

2005 Scandinavian Journal of Primary Health Care 23 (4); 242 – 247

<http://www.scopus.com/inward/record.url?eid=2-s2.0-32344434669&partnerID=40>

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Objectives. To explore causal attributions among women with chronic fatigue syndrome (CFS). Design. Qualitative study where data from individual semi-structured interviews were analysed according to Malterud's systematic text condensation. Setting. Bergen, Norway. Subjects. A purposeful sample of eight women aged 25-55, recruited among members of a self-help organization. Main outcome measures. Accounts of causal attribution for CFS among the informants, focusing on gender. Results. The participants agreed that their way of living could have increased the vulnerability of their resistance resources. Pressure they put upon themselves, workload burdens without subsequent relaxation, emotional conflicts, or preparing for assumed problem-solving were mentioned as gendered dimensions. They presented different explanations regarding potential triggers encountering their fragile immune systems, most often a virus infection. The participants thought women might have a weaker immune system than men, or that CFS was caused by a virus that women are more likely to catch. In their experience, their symptoms were activated when people put pressure on them, such that they might be nervous as to whether they could live up to the demands of their surroundings, and in the case of emotional strain related to family and work. Conclusion. More studies are needed exploring hypotheses concerning the complex interplay between molecular predispositions and more or less gendered lifestyle issues in CFS. Doctors need to challenge their strong beliefs regarding medically unexplained conditions, where facts still remain unresolved. Recognizing this, the doctor may provide realistic support and advice, and contribute to the establishment of common ground for understanding and managing the condition. © 2005 Taylor & Francis.

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The relationships among coping styles and fatigue in an ethnically diverse sample

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-26644437204&partnerID=40>

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The present study focused on coping strategies among African Americans, Latinos, and European Americans with chronic fatigue syndrome (CFS) and idiopathic chronic fatigue (ICF). The coping strategies examined were measured by using the COPE Scales, which assess Seeking Emotional Social Support, Positive Reinterpretation and Growth, Acceptance, Denial, Turning to Religion, Behavioral Disengagement, and Focusing on and Venting Emotions. In addition, the four coping strategies specifically designed for people with CFS, including maintaining activity, accommodating to the illness, focusing on symptoms, and information-seeking, were used in this study. It was hypothesized that African Americans and Latinos in comparison to European Americans would be more likely to use religious coping, behavioral disengagement, and denial. As predicted, African Americans were significantly more likely to turn to religion than European Americans, and Latinos and African Americans used denial significantly more often than European Americans. An additional finding was that focusing on symptoms was associated with greater fatigue and more physical disability among African Americans. Within the Latino sample, acceptance was related to greater fatigue and less physical disability, and greater optimism predicted less mental disability. Among European American participants, maintaining activity was related to less mental disability, whereas accommodating to the illness predicted more physical disability. These results indicate that coping varies among various

ethnic groups with CFS and ICF; however, denial is consistently related to less adaptive outcomes. Therefore, healthcare professionals should find ways to reduce patient use of denial and promote alternative strategies for managing life events. © 2005 Taylor & Francis.

Nijs J., Van de Putte K., Louckx F., De Meirleir K.

Employment status in chronic fatigue syndrome. A cross-sectional study examining the value of exercise testing and self-reported measures for the assessment of employment status

2005 Clinical Rehabilitation 19 (8); 895 - 899

<http://www.scopus.com/inward/record.url?eid=2-s2.0-28444477028&partnerID=40>

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Objective: To examine the value of exercise testing and self-reported disability for the assessment of employment status in patients with chronic fatigue syndrome. Design: Cross-sectional observational study. Setting: A university-based chronic fatigue clinic. Subjects: Fifty-four consecutive, Flemish, employed (not self-employed) chronic fatigue syndrome patients (49/54 female). Interventions: Not applicable. Main outcome measures: Participants were questioned about their current and premorbid employment status, filled in the Chronic Fatigue Syndrome Activities and Participation Questionnaire (CFS-APQ), the Medical Outcomes Short Form 36 Health Status Survey (SF-36), and performed a maximal exercise test on a bicycle ergometer with continuous monitoring of cardiorespiratory variables. Results: A significant association was observed between the current employment rate and two SF-36 subscales (i.e., role limitations due to physical functioning and social functioning; $\rho = 0.39$ and 0.35 respectively) ($n = 54$). Analysing only the female chronic fatigue syndrome patients ($n = 49$), the current employment rate correlated significantly with the peak workload ($\rho = 0.38$). Conclusions: The associations between either exercise testing or self-reported disability and employment status are too weak to predict employment status. © 2005 Edward Arnold (Publishers) Ltd.

Lombaard A., Mouton J.

Chronic fatigue syndrome, the body and the self: A qualitative analysis

2005 South African Journal of Psychology 35 (2); 286 - 307

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847758746&partnerID=40>

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In a study directed towards the development of a greater understanding of the subjective illness experience of those who suffer from Chronic Fatigue Syndrome (CFS), we identified the sufferer's relationship with the body as one of the dimensions of the self most affected by CFS. We found that the profound changes instigated by CFS transform the relationship between the self and the body into a frontline where conflict prevails and inner dissension threaten. Participants' experiences fortunately revealed that such discord can be attenuated when the self makes it its personal responsibility to listen attentively to the body and to then respond to it in a way that will support a sensible balance between activity and restriction. © Psychological Society of South Africa. All rights reserved.

Friedberg F., Leung D.W., Quick J.

Do support groups help people with chronic fatigue syndrome and fibromyalgia? A comparison of active and inactive members

2005 Journal of Rheumatology 32 (12); 2416 – 2420

<http://www.scopus.com/inward/record.url?eid=2-s2.0-28844449133&partnerID=40>

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Objective. To examine the benefits and problems of a chronic fatigue syndrome (CFS) and fibromyalgia (FM) support organization as reported by its participants. **Methods.** Active members (n = 32) and inactive members or dropouts (n = 135) of a regional support organization for people with CFS and FM completed a 26 item questionnaire by telephone interview or by self-completion and postal return. **Results.** The most frequently endorsed benefits of membership were illness legitimization (67.8%), finding out helpful new information (66.4%), and feeling understood by others (62.2%). Lower frequency endorsements were given to: helped to find (35.0%) or deal with (38.5%) doctors, and helped to improve my illness (36.4%). The most frequently reported reasons for dropping out were inconvenient location (37.8%) or time (37.0%), too much negative talk or complaining (33.3%), too sick to attend (28.8%), and illness or coping improvement (29.6% each). The active-member group showed significantly higher ($p < 0.04$) symptom severity scores and less illness improvement ($p < 0.01$) in comparison to the inactive/dropout group. **Conclusion.** This cross-sectional study suggests that support groups for CFS are viewed as helpful by participants on a number of illness related issues. On the other hand, active members reported greater symptom severity and less illness improvement than inactive members or dropouts.

Schoofs N., Bambini D., Ronning P., Bielak E., Woehl J.

Death of a lifestyle: the effects of social support and healthcare support on the quality of life of persons with fibromyalgia and/or chronic fatigue syndrome.

2004 Orthopaedic nursing / National Association of Orthopaedic Nurses 23 (6); 364 – 374

<http://www.scopus.com/inward/record.url?eid=2-s2.0-14744271424&partnerID=40>

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PURPOSE: The purpose of this study was to investigate how social support and healthcare support affect the quality of life of persons with fibromyalgia and chronic fatigue syndrome. **METHOD:** A constant comparison method was used for the qualitative portion of the research and descriptive correlational methods were used for the quantitative portion. **CONCLUSION:** This mixed design research study suggested that social support, unlike healthcare support, is related to Quality of Life (QOL). It was also evident that subjects suffering from CFS and/or FMS do not experience high levels of social support.

Raine R., Carter S., Sensky T., Black N.

General practitioners' perceptions of chronic fatigue syndrome and beliefs about its management, compared with irritable bowel syndrome: Qualitative study

2004 British Medical Journal 328 (7452); 1354 – 1356

<http://www.scopus.com/inward/record.url?eid=2-s2.0-2942532498&partnerID=40>

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Objectives: To compare general practitioners' perceptions of chronic fatigue syndrome and irritable bowel syndrome and to consider the implications of their perceptions for treatment. **Design:** Qualitative analysis of transcripts of group discussions. **Participants and setting:** A randomly selected sample of 46

general practitioners in England. Results: The participants tended to stereotype patients with chronic fatigue syndrome as having certain undesirable traits. This stereotyping was due to the lack of a precise bodily location; the reclassification of the syndrome over time; transgression of social roles, with patients seen as failing to conform to the work ethic and "sick role"; and conflict between doctor and patient over causes and management. These factors led to difficulties for many general practitioners in managing patients with chronic fatigue syndrome. For both conditions many participants would not consider referral for mental health interventions, even though the doctors recognised social and psychological factors, because they were not familiar with the interventions or thought them unavailable or unnecessary. Conclusions: Barriers to the effective clinical management of patients with irritable bowel syndrome and chronic fatigue syndrome are partly due to doctors' beliefs, which result in negative stereotyping of patients with chronic fatigue syndrome and the use of management strategies for both syndromes that may not take into account the best available evidence.

Prins J.B., Bos E., Huibers M.J.H., Servaes P., Van Der Werf S.P., Van Der Meer J.W.M., Bleijenberg G. Social support and the persistence of complaints in chronic fatigue syndrome

2004 Psychotherapy and Psychosomatics 73 (3); 174 – 182

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1842612490&partnerID=40>

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Background: Several studies suggested that the surroundings of chronic fatigue syndrome (CFS) patients are of importance in the persistence of complaints. Contrary to what was expected, participation in support groups has not led to clinical improvement. The purpose of the present study was to describe social support in CFS patients as compared with other fatigued and nonfatigued groups. Further, changes in social support and the influence of social support on the course of CFS over a period of more than 1 year were studied in patients with and without treatment. Methods: Baseline data were assessed in 270 CFS patients, 150 disease-free breast cancer patients, 151 fatigued employees on sick-leave and 108 healthy subjects using the Social Support List and Significant Others Scale. CFS patients were followed in cognitive behaviour therapy (CBT), guided support groups and natural course at 8 and 14 months. Results: CFS patients and fatigued employees reported more negative interactions and insufficiency of supporting interactions than cancer patients and healthy controls. No differences in frequency of supporting interactions were found. Negative interactions decreased significantly after treatment with CBT, but did not change in support groups or natural course. In the natural course, higher fatigue severity at 8 months was predicted by more negative interactions at baseline. Conclusions: In CFS patients and fatigued employees, social support is worse than in disease-free cancer patients and healthy controls. Lack of social support was identified as a new factor in the model of perpetuating factors of fatigue severity and functional impairment in CFS. Copyright © 2004 S. Karger AG, Basel.

McCue P.

CFS/ME and mental health diagnoses: A qualitative approach to assessing the experiences of women who have now recovered

2004 Clinical Effectiveness in Nursing 8 (03-Apr); 194 – 201

<http://www.scopus.com/inward/record.url?eid=2-s2.0-24344490282&partnerID=40>

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Despite much research in recent years there still remains much doubt as to what causes CFS, and the role that mental health disorders play in its aetiology and perpetuation. The purpose of this study was to assess the illness experiences of a cohort of women who had recovered from Chronic Fatigue Syndrome (CFS) or Myalgic Encephalomyelitis (ME) in order to examine the extent to which the

diagnoses they were given took a mental health perspective, and whether or not it was accepted that they were suffering a genuine illness. This was a qualitative study using Grounded Theory, with a sample of 14 female participants who had previously had CFS but considered themselves to be substantially or totally recovered from this illness. It was found that the participants experienced substantial problems with regard to diagnosis, with health care professionals often ignoring their physical symptoms. Similarly they encountered problems of acceptance and belief in terms of having a genuine illness. The findings are further discussed in terms of concomitant stigma and bias towards mental health diagnoses for women generally. © 2005 Elsevier Ltd. All rights reserved.

MacKian S.

Mapping reflexive communities: Visualizing the geographies of emotion

2004 Social and Cultural Geography 5 (4); 615 – 631

<http://www.scopus.com/inward/record.url?eid=2-s2.0-11944252081&partnerID=40>

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Whereas 'simple modernity' was characterized by objective space, the grid of the map, and a removal of all subjective symbols or signs, 'reflexive modernity' is characterized by a re-subjectivization of space. Within this space 'reflexive communities' emerge to make sense of emotions and experiences, reflecting particular ways of behaving, thinking and being. As geographers one task facing us now is to visualize and map the spaces of reflexive modernization. This paper presents a means of visualizing the text of emotions uncovered in the research encounter—a way of 'mapping' reflexive communities—and shows how we can articulate, negotiate and represent, complex emotional landscapes. The 'maps'-which draw on spatial metaphors that permeate everyday emotions—such as 'distancing' ourselves, 'engaging', 'joining', 'feeling detached', 'embracing'—were developed initially through analysis of in-depth interviews with long-term sufferers of myalgic encephalomyelitis (ME). Although the key focus of the paper is the experience of long-term illness, the method of visualizing emotional geographies of everyday life could be applied in any number of fields. As such, it adds to the search across the social sciences for understanding the reflexive nature of contemporary space. © 2004 Taylor & Francis Ltd.

Looper K.J., Kirmayer L.J.

Perceived stigma in functional somatic syndromes and comparable medical conditions

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-7044270771&partnerID=40>

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Objective To determine if patients with functional somatic syndromes (FSS) perceive greater levels of stigma than patients with comparable medical conditions that have a clear medical pathology. Methods Patients with chronic fatigue syndrome (CFS), fibromyalgia (FM), or irritable bowel syndrome (IBS) were compared to multiple sclerosis (MS), rheumatoid arthritis (RA), and inflammatory bowel disease (IBS), respectively. Results There were greater levels of perceived stigma in the combined group of FSS compared to the medical control group. When each FSS was compared to its matched control group, only CFS had a higher level of perceived stigma. These results remained when controlling for other variables relevant to stigma. Conclusions The higher level of perceived stigma in CFS may be due to the ambiguity of its status as a medical condition. The absence of this effect in FM and IBS is consistent with a greater level of acceptance of these disorders as medical illnesses. © 2004 Elsevier Inc. All rights reserved.

Cervera C., Alegre J., Ruiz E., Vazquez A., Armadans L., Garcia-Quintana A.M., Aleman C., Fernandez De Sevilla T.

Employment status and financial repercussions in 60 patients with chronic fatigue syndrome in Spain: Utility of the Fatigue Impact Scale

2004 Journal of Chronic Fatigue Syndrome 12 (2); 35 – 45

<http://www.scopus.com/inward/record.url?eid=2-s2.0-22844436240&partnerID=40>

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Chronic fatigue syndrome (CFS) is a disabling disorder with implications in employment status. We enrolled 60 patients who fulfilled the CDC diagnostic criteria of Holmes and those of Fukuda. All patients underwent a protocol involving a structured questionnaire to record diagnostic criteria items, clinical features of fatigue, social features and associated symptoms; application of the Fatigue Impact Scale (FIS); an employment repercussion questionnaire; and information on evolution of the symptoms. Statistical comparisons were performed with the Mann-Whitney U test and correlations with the Spearman test. A close correlation was found between work inactivity and higher scores in the FIS cognitive dimension. Patient age and duration of symptoms also correlated with high cognitive scores. Chronic fatigue syndrome patients report a considerable decrease in quality of life, and most of them have work limitations, particularly those with poor overall FIS scores and cognitive function scores. © 2004 by The Haworth Press, Inc. All rights reserved.

Brocki J.M., Wearden A.J.

Defending the self in CFS: Identifying the enemy - An interpretative phenomenological analysis

2004 Psychology and Health 19 (SUPPL. 1); 27 – 28

<http://www.scopus.com/inward/record.url?eid=2-s2.0-22744448184&partnerID=40>

Objectives: To use qualitative research methods to carry out an in-depth examination of the beliefs that patients with chronic fatigue syndrome (CFS, also known as ME) and their spouses hold about the illness, in particular contrasting how the condition is understood through the evidence of personal experience and by others. Methods: Leventhal's self regulatory model (Leventhal et al., 1984, 1997) was used as a guide to construct semi-structured interviews which were carried out with two CFS patients and their spouses. Interview transcripts were analysed using interpretative phenomenological analysis (IPA). Results: Four major themes were identified: 1. 'Worker not a shirker' - portrayal of the patient struggling to fight personifications of the illness; inconsistencies in identifying effective methods of management. 2. 'He felt relieved he had a label, he thought he was cracking up' - reactions to diagnosis; dealings with the medical community. 3. 'My ex-wife says it's attention seeking' - perceptions of others; legitimisation of sick role status. 4. 'Do you think people with chronic diarrhoea have diarrhoea for all their lives?' - expectations for the future. Conclusions: The effects on self-concept in CFS/ME and perceptions of others' opinions is discussed. It is suggested that this may have implications for treatment uptake and compliance in CFS/ME. The use of IPA methodology facilitated the distinction of individuals' complex reasoning processes whilst enabling the identification of patterns across accounts.

Asbring P., Narvanen A.-L.

Patient power and control: A study of women with uncertain illness trajectories

2004 Qualitative Health Research 14 (2); 226 – 240

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1542289576&partnerID=40>

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The authors interviewed 12 women diagnosed with chronic fatigue syndrome and 13 with fibromyalgia with the aim of determining the strategies they perceive themselves as using to gain control over their

situation during the health care process. The results highlight various strategies that the women report applying to find a way of managing the illness and to influence caregivers. They describe, for example, how they try to gain control over their situation by acquiring knowledge about the illness. The women also describe various power strategies they use in their interaction with the caregivers to take command of their situation, namely exiting, noncompliance, confrontation, persuasion/insistence, making demands, and demonstrative distancing. © 2004 Sage Publications.

Woolley J., Allen R., Wessely S.
Alcohol use in chronic fatigue syndrome

2004 Journal of Psychosomatic Research 56 (2); 203 – 206

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1542358042&partnerID=40>

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Objective: To examine the anecdotal observation that patients with chronic fatigue syndrome develop alcohol intolerance. Methods: A consecutive case series of 114 patients fulfilling UK criteria for chronic fatigue syndrome referred to a specialist clinic. Self-reported alcohol use pre- and postdiagnosis, fatigue symptoms and comorbidity measures were collected. Results: Two-thirds reduced alcohol intake. The most common reasons were increased tiredness after drinking (67%), increased nausea (33%), exacerbated hangovers (23%) and sleep disturbance (24%). One-third of the subjects also stopped drinking because "it seemed sensible." Some had been advised to avoid alcohol, but the majority (66%) did so on the basis of personal experience. Conclusion: Our data supports the anecdotal belief that chronic fatigue syndrome patients reduce or cease alcohol intake. This is associated with greater impairment in employment, leisure and social domains of function, and may hint at psycho-pathophysiological processes in common with other conditions that result in alcohol intolerance. © 2004 Elsevier Inc. All rights reserved.

Treatment

Zhang K.-J.

Tuina plus acupuncture for chronic fatigue syndrome: A report of 87 cases

2009 Journal of Acupuncture and Tuina Science 7 (2); 102 – 104

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65449169626&partnerID=40>

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[No abstract available]

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Associations between pet ownership and self-reported health status in people suffering from chronic fatigue syndrome

2009 Journal of Alternative and Complementary Medicine 15 (4); 407 – 413

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65549152348&partnerID=40>

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Objective: This study explored the association between pet ownership and self-reported health in people suffering from chronic fatigue syndrome (CFS). Methods: One hundred and ninety-three (193) people with medically diagnosed CFS completed a postal survey designed to collect information on illness severity, physical and psychologic health, and pet ownership practices. Results: Most of the participants were female (72.0%), over 45 years of age (57.1%) and married (41.1%) with no children (63.1%). Pets were owned by 58.3% of the sample, with dogs and cats being the most commonly kept types of companion animal. The general health of the participants was discovered to be poor, as assessed by scores on the Chalder Fatigue Questionnaire (CFQ), General Health Questionnaire-12 (GHQ-12), and Short-Form-36 (SF-36) health survey. Pet ownership was not significantly associated with scores on the CFQ, GHQ-12, or SF-36 scales, although pet owners considered their animals to offer them a range of health benefits, notably those associated with mental well-being. Conclusions: Overall, findings suggest no statistically significant association between pet ownership and self-reported health in people with CFS. Nonetheless, people suffering from this condition believe that their pets have the potential to enhance quality of life. Although animals should not be regarded as a panacea for people with long-term conditions such as CFS, they may, nonetheless, serve a valuable, and currently underutilized, role in promoting well-being, whether in their own right, or in conjunction with more traditional forms of therapy. © 2009 Copyright 2009, Mary Ann Liebert, Inc.

Wang J.-H., Chai T.-Q., Lin G.-H., Luo L.

Effect of the intelligent-turtle massage on the physical symptoms and immune functions in patients with chronic fatigue syndrome

2009 Journal of Traditional Chinese Medicine 29 (1); 24 – 28

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To evaluate the effects of the intelligent-turtle massage on the physical symptoms and immune functions in patients with chronic fatigue syndrome (CFS). Methods: 182 cases of CFS were randomly divided into an experimental group of 91 cases treated by the intelligent-turtle massage, and a control group of 91 cases treated with the conventional massage method. After 2 courses of treatment, the therapeutic effects were statistically analyzed with the accumulated score for the

improved clinical symptoms; and the changes of IgA, IgM and IgG were compared in 96 cases. Results: There was a significant difference between the two groups in the accumulated scores for improvement of the symptoms ($P < 0.05$). A remarkable difference was found in the therapeutic effect. And there was a significant difference in the IgA, IgM and IgG levels between the two groups ($P < 0.05$). Conclusion: The intelligent-turtle massage is an effective therapy for relieving the physical symptoms of CFS, and it may show certain effects on the immune functions.

Walker K., Lindner H., Noonan M.

The role of coping in the relationship between depression and illness severity in chronic fatigue syndrome

2009 Journal of Allied Health 38 (2); 91 - 99

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The self-regulatory model (SRM) proposes that both cognitive and emotional illness representations influence the coping processes adopted in response to an illness. Aim: This study used the SRM to explore the role of coping in the relationship between depression and self-appraisals of illness severity in a population of patients with chronic fatigue syndrome (CFS). Methods: The sample comprised 156 participants, 34 men and 121 women, aged between 18 and 78 yrs, who had been medically diagnosed with CFS. Participants were asked to complete three questionnaires: the Cardiac Depression Scale, Ways of Coping Questionnaire, and Severity Subscale of the Illness Perceptions Questionnaire-Revised. Results: Analyses revealed that almost 70% of the participants were moderately or severely depressed. Additionally, two particular subscales, social support seeking and positive reappraisals, emerged as positively contributing to self-appraisals of illness severity ($\hat{I}^2 = 0.20$ [$p < 0.05$] and $\hat{I}^2 = 0.21$ [$p < 0.05$], respectively), thereby supporting the SRM. Furthermore, results indicated that a combination of depression and coping was a better predictor of illness severity than depression alone, accounting for 22% of the variance compared with 8%, respectively. Conclusions: The findings suggest that focusing on depression, and particularly coping styles, during treatment interventions could have important implications for therapeutic interventions. This could lead to better treatment strategies for health professionals who work with patients with CFS. J Allied Health 2009; 38:91-99.

Scheeres K., Knoop H., van der Jos M., Bleijenberg G.

Clinical assessment of the physical activity pattern of chronic fatigue syndrome patients: A validation of three methods

2009 Health and Quality of Life Outcomes 7

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65149096164&partnerID=40>

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Background: Effective treatment of chronic fatigue syndrome (CFS) with cognitive behavioural therapy (CBT) relies on a correct classification of so called 'fluctuating active' versus 'passive' patients. For successful treatment with CBT it is especially important to recognise the passive patients and give them a tailored treatment protocol. In the present study it was evaluated whether CFS patient's physical activity pattern can be assessed most accurately with the 'Activity Pattern

Interview' (API), the International Physical Activity Questionnaire (IPAQ) or the CFS-Activity Questionnaire (CFS-AQ). Methods: The three instruments were validated compared to actometers. Actometers are until now the best and most objective instrument to measure physical activity, but they are too expensive and time consuming for most clinical practice settings. In total 226 CFS patients enrolled for CBT therapy answered the API at intake and filled in the two questionnaires. Directly after intake they wore the actometer for two weeks. Based on receiver operating characteristic (ROC) curves the validity of the three methods were assessed and compared. Results: Both the API and the two questionnaires had an acceptable validity (0.64 to 0.71). None of the three instruments was significantly better than the others. The proportion of false predictions was rather high for all three instrument. The IPAQ had the highest proportion of correct passive predictions (sensitivity 70.1%). Conclusion: The validity of all three instruments appeared to be fair, and all showed rather high proportions of false classifications. Hence in fact none of the tested instruments could really be called satisfactory. Because the IPAQ showed to be the best in correctly predicting 'passive' CFS patients, which is most essentially related to treatment results, it was concluded that the IPAQ is the preferable alternative for an actometer when treating CFS patients in clinical practice. © 2009 Scheeres et al; licensee BioMed Central Ltd.

Lin J.-M.S., Brimmer D.J., Boneva R.S., Jones J.F., Reeves W.C.
Barriers to healthcare utilization in fatiguing illness: A population-based study in Georgia
2009 BMC Health Services Research 9
<http://www.scopus.com/inward/record.url?eid=2-s2.0-61849093615&partnerID=40>

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Background. The purpose of this study was to determine the prevalence of barriers to healthcare utilization in persons with fatiguing illness and describe its association with socio-demographics, the number of health conditions, and frequency of healthcare utilization. Furthermore, we sought to identify what types of barriers interfered with healthcare utilization and why they occurred. **Methods.** In a cross-sectional population-based survey, 780 subjects, 112 of them with chronic fatigue syndrome (CFS), completed a healthcare utilization questionnaire. Text analysis was used to create the emerging themes from verbatim responses regarding barriers to healthcare utilization. Multiple logistic regression was performed to examine the association between barriers to healthcare utilization and other factors. **Results.** Forty percent of subjects reported at least one barrier to healthcare utilization. Of 112 subjects with CFS, 55% reported at least one barrier to healthcare utilization. Fatiguing status, reported duration of fatigue, insurance, and BMI were significant risk factors for barriers to healthcare utilization. After adjusting for socio-demographics, medication use, the number of health problems, and frequency of healthcare utilization, fatiguing status remained significantly associated with barriers to healthcare utilization. Subjects with CFS were nearly 4 times more likely to forego needed healthcare during the preceding year than non-fatigued subjects while those with insufficient fatigue (ISF) were nearly 3 times more likely. Three domains emerged from text analysis on barriers to healthcare utilization: 1) accessibility; 2) knowledge-attitudes-beliefs (KABs); and, 3) healthcare system. CFS and reported duration of fatigue were significantly associated with each of these domains. Persons with CFS reported high levels of healthcare utilization barriers for each domain: accessibility (34%), healthcare system (25%), and KABs (19%). In further examination of barrier domains to healthcare utilization, compared to non-fatigued persons adjusted ORs for CFS having "accessibility", "KAB" and "Healthcare System" barrier domains decreased by 40%, 30%, and 19%, respectively. **Conclusion.** Barriers to healthcare utilization pose a significant problem in persons with fatiguing illnesses. Study results suggested two-fold implications: a symptom-targeted model focusing on symptoms associated with fatigue; and an interactive model requiring efforts from patients and providers to improve interactions between them by reducing barriers in accessibility, KABs, and healthcare system.

Kumar A., Garg R.

Protective effects of antidepressants against chronic fatigue syndrome - Induced behavioral changes and biochemical alterations

2009 Fundamental and Clinical Pharmacology 23 (1); 89 – 95

<http://www.scopus.com/inward/record.url?eid=2-s2.0-61349112061&partnerID=40>

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Chronic fatigue syndrome (CFS) is characterized by profound fatigue, which substantially interferes with daily activities. The aim of this study was to explore the protective effects of antidepressants in an animal model of CFS in mice. Male albino mice were forced to swim individually for a period of 6-min session each for 7 days. Imipramine (10 and 20 mg/kg), desipramine (10 and 20 mg/kg) and citalopram (5 and 10 mg/kg) were administered 30 min before forced swimming test on each day. Various behavior tests (immobility time, locomotor activity, anxiety-like behavior by plus maze and mirror chamber) followed by biochemical parameters (lipid peroxidation, reduced glutathione, catalase and nitrite level) were assessed in chronic stressed mice. Chronic forced swimming for 7 days significantly caused increase in immobility period, impairment in locomotor activity, anxiety-like behavior, and oxidative stress (raised lipid peroxidation, nitrite activity and reduced glutathione and catalase activity) as compared with naïve mice ($P < 0.05$). Seven days of pretreatment with imipramine (10 and 20 mg/kg), desipramine (10 and 20 mg/kg), and citalopram (5 and 10 mg/kg) significantly reduced immobility time, improved locomotor activity and anti-anxiety effect (in both plus maze and mirror chamber test), and attenuated oxidative stress in chronic stressed mice as compared with control (chronic fatigues) ($P < 0.05$). These results suggested that these drugs have protective effect and could be used in the management of chronic fatigue like conditions. © 2008 Soci  Fran aise de Pharmacologie et de Th rapeutique.

Gordon B., Lubitz L.

Promising outcomes of an adolescent chronic fatigue syndrome inpatient programme

2009 Journal of Paediatrics and Child Health 45 (5); 286 – 290

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65449181103&partnerID=40>

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Introduction: Chronic fatigue syndrome (CFS) is a condition of prolonged and disabling fatigue, which is accompanied by characteristic constitutional and neuropsychiatric symptoms. In children and adolescents, this condition occurring at a developmentally vulnerable time adds to the disability affecting self-concept, autonomy, body image, socialisation, sexuality and academic problems. This case series looks at the effects of a graded exercise programme on physical outcomes, fatigue and mental state in an adolescent population. Methods: Data sets from 16 adolescents who completed combined exercise training as part of the 4-week inpatient intensive CFS programme at the Austin Hospital, Melbourne were analysed. All patients completed an exercise assessment and three questionnaires before beginning any training. A paediatrician (LL) confirmed the diagnosis according to the Fukuda criteria in all patients. Exercise was carefully supervised and prescribed daily by an exercise physiologist (BG) according to each individual's ability and response with the basic aim of increasing exercise tolerance and improving muscle strength and endurance. Results: There was an 18% improvement in volitional time to fatigue ($P = 0.02$) and 17% improvement in peak oxygen uptake (VO_{2peak}) ($P = 0.01$). Upper body strength and function improved with a remarkable 70% increase in the number of push-ups. Fatigue severity was reported to improve by 13% ($P = 0.01$) and depression index improved significantly by 42% ($P = 0.02$). Conclusions: The significance of these improvements cannot be underestimated as an improvement in physical capacity through increased time to fatigue and less severe fatigue allows adolescents to resume school, social and

family activities. © 2009 Paediatrics and Child Health Division (Royal Australasian College of Physicians).

Friedberg F., Sohl S.J.

Longitudinal change in chronic fatigue syndrome: What home-based assessments reveal

2009 Journal of Behavioral Medicine 32 (2); 209 – 218

<http://www.scopus.com/inward/record.url?eid=2-s2.0-62949095935&partnerID=40>

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The purpose of this 2-year prospective study was to compare standard self-report and ecologically-based outcome measures in patients with chronic fatigue syndrome (CFS). Standard measures assessed physical function, fatigue impact, psychological variables, and global impression of change ratings. Ecological measures included actigraphy, a structured activity record, and an electronic fatigue/energy diary. Results for this high functioning sample (N = 75) revealed that self-report global improvement was significantly associated with lower momentary fatigue and fatigue impact, and a higher frequency of standing up (at home), but not with actigraphy or psychological variables. However, actigraphy change was significantly correlated with change in self-report physical function. At follow-up, only a small minority (<20%) scored in the healthy adult range for fatigue impact and physical function. The findings suggest that home-based measures of symptom severity and physical functioning may provide evidence of change (or lack of change) that is important for interpreting standard self-report outcomes in CFS. © 2008 Springer Science+Business Media, LLC.

Friedberg F., Sohl S.

Cognitive-behavior therapy in chronic fatigue syndrome: Is improvement related to increased physical activity?

2009 Journal of Clinical Psychology 65 (4); 423 – 442

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67449164808&partnerID=40>

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This multiple case study of cognitive-behavioral treatment (CBT) for chronic fatigue syndrome (CFS) compared self-report and behavioral outcomes. Eleven relatively high-functioning participants with CFS received 6-32 sessions of outpatient graded-activity oriented CBT. Self-report outcomes included measures of fatigue impact, physical function, depression, anxiety, and global change. Behavioral outcomes included actigraphy and the 6-minute walking test. Global change ratings were very much improved (n52), much improved (n52), improved (n55), and no change (n52). Of those reporting improvement, clinically significant actigraphy increases (n53) and decreases (n54) were found, as well as no significant change (n52). The nature of clinical improvement in CBT trials for high-functioning CFS patients may be more ambiguous than that postulated by the cognitive-behavioral model. © 2009 Wiley Periodicals, Inc.

Dai D.-C., Fang M., Yan J.-T., Jiang S.-Y., Liu K.-P.

Tuina intervention and sleep and emotional disorders due to chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-67049143099&partnerID=40>

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Objective: To study the tuina effect on sleep disorder and emotional problems of chronic fatigue syndrome (CFS) cases. Method: Thirty CFS cases were treated in the treatment group, by applying one-thumb pushing, rolling and pressing-kneading manipulations along the Governor Vessel,

Bladder and Yangming Meridians. The intended major points include Fengfu (GV 16), Yaoyangguan (GV 3), Xinshu (BL 15), Pishu (BL 20), Ganshu (BL 18), Hegu (LI 4) and Taixi (KI 3). The treatment was done once every other day; 10 times constitute a course of treatment. Another 30 healthy cases were selected in the control group, without any intervention. The sleep quality and mental state in the two groups were evaluated by PSQI, HAMA and HAMD. In addition, the pre-treatment and post-treatment score changes were observed. Results: Before treatment, the total score of PSQI, sleep quality, time of falling asleep, sleep efficiency, sleep disorder, daytime functional impairment, and scores of HAMD and HAMA in treatment group were all substantially higher than the control group ($P < 0.01$). After 10 tuina treatments, the total score of PSQI, time of falling asleep, sleep disorder and daytime functional impairment as well as scores of HAMD and HAMA in treatment group were significantly changed, compared with before treatment, $P < 0.05$. Conclusion: Those with CFS may present with sleep disorder and mental or psychological abnormality, tuina can improve their sleep quality and adjust their mental conditions. © Shanghai Research Institute of Acupuncture and Meridian and Springer-Verlag GmbH 2009.

Cho J.H., Cho C.K., Shin J.W., Son J.Y., Kang W., Son C.G.
Myelophil, an extract mix of Astragali Radix and Salviae Radix, ameliorates chronic fatigue: A randomised, double-blind, controlled pilot study

2009 Complementary Therapies in Medicine 17 (3); 141 – 146

<http://www.scopus.com/inward/record.url?eid=2-s2.0-65049088110&partnerID=40>

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Objectives: To investigate the anti-fatigue effects of Myelophil, an extract of a mix of Astragali Radix and Salviae Radix, which has been used to treat patients with chronic fatigue. Subjects and design: A randomised, double-blind, controlled clinical trial was performed with 36 adults who complained of chronic fatigue. The subjects were divided among a control group and low- and high-dose groups (3 or 6 g of oral Myelophil per day, respectively) and were monitored for 4 weeks. Fatigue severity was subjectively characterised, and the expression of 42 cytokines was evaluated using an antibody array. Results: Myelophil administration (3 g per day) significantly decreased the fatigue severity score compared with the control ($p < 0.05$). No changes were noted in cytokine expression. Conclusions: Myelophil appears to have a pharmacological effect against fatigue, suggesting the clinical relevance of the traditional medicinal plants, Astragalus membranaceus and Salvia miltiorrhiza. © 2008 Elsevier Ltd. All rights reserved.

Chew-Graham C., Dixon R., Shaw J.W., Smyth N., Lovell K., Peters S.
Practice Nurses' views of their role in the management of Chronic Fatigue Syndrome/Myalgic Encephalitis: A qualitative study

2009 BMC Nursing 8

<http://www.scopus.com/inward/record.url?eid=2-s2.0-60549088286&partnerID=40>

School of Community-Based Medicine, University of Manchester, Manchester, M13 9PL, United Kingdom; School of Psychological Sciences, University of Manchester, Manchester, M13 9PL, United Kingdom; School of Nursing, Midwifery and Social Work, University of Manchester, Manchester, M13 9PL, United Kingdom Background.

NICE guidelines suggest that patients with Chronic Fatigue Syndrome/Myalgic Encephalitis (CFS/ME) should be managed in Primary Care. Practice Nurses are increasingly being involved in the management of long-term conditions, so are likely to also have a growing role in managing CFS/ME. However their attitudes to, and experiences of patients with CFS/ME and its management must be explored to understand what barriers may exist in developing their role for this group of patients. The aim of this study was to explore Practice Nurses' understanding and beliefs about CFS/ME and

its management. Methods. Semi-structured interviews with 29 Practice Nurses. Interviews were transcribed verbatim and an iterative approach used to develop themes from the dataset. Results. Practice nurses had limited understanding about CFS/ME which had been largely gained through contact with patients, friends, personal experiences and the media rather than formal training. They had difficulty seeing CFS/ME as a long term condition. They did identify a potential role they could have in management of CFS/ME but devalued their own skills in psychological intervention, and suggested counselling would be an appropriate therapeutic option. They recognised a need for further training and on going supervision from both medical and psychological colleagues. Some viewed the condition as contentious and held pejorative views about CFS/ME. Such scepticism and negative attitudes will be a significant barrier to the management of patients with CFS/ME in primary care. Conclusion. The current role of Practice Nurses in the ongoing management of patients with CFS/ME is limited. Practice Nurses have little understanding of the evidence-base for treatment of CFS/ME, particularly psychological therapies, describing management options in terms of advice giving, self-help or counselling. Practice Nurses largely welcomed the potential development of their role in this area, but identified barriers and training needs which must be addressed to enable them to feel confident managing of patients with this condition. Training must begin by addressing negative attitudes to patients with CFS/ME. © 2009 Chew-Graham et al; licensee BioMed Central Ltd.

Belgamwar R.B., Jorsh M.S., Knisely-Marpole A., Snowden H., Mayall E., Singhal A., Jones J.M.
Multidisciplinary group treatment for chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-63249098567&partnerID=40>

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It is estimated that between 0.2 and 0.4 per cent of the population suffer from chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Service provision varies across the UK, and while there is a good evidence for the efficacy of cognitive behavioural therapy and graded exercise programmes, the evidence for group interventions is still limited. Here, the authors describe the results of their service evaluation of a group treatment programme for CFS/ME.

Wu Y.-Z., Ding Y.-S., Xu H.-A., Shi J.-L., Zhu B.-H.

SVM based chronic fatigue syndrome evaluation for intelligent garment

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Chronic fatigue syndrome (CFS) also called sub-health is a serious and complex problem for modern people all over the world. But the methods of CFS diagnosis up to now are very elementary. This paper tries to establish a CFS evaluation model based on human body's vital signals, especially ECG. Firstly, an intelligent garment oriented physiological signal capturing and processing platform is proposed. Then, a multi-class SVM-based strategy to render a diagnosis between various degrees of CFS is constructed. Based on the ISNI-DHU CFS database we set up, the results show that the diagnosis model achieve high classification accuracy, at 97.4% of average accuracy, and heartbeat parameters can be effectively used to evaluation of CFS. © 2008 IEEE.

Walach H., Bosch H., Lewith G., Naumann J., Schwarzer B., Falk S., Kohls N., Haraldsson E., Wiesendanger H., Nordmann A., Tomasson H., Prescott P., Bucher H.C.
Effectiveness of distant healing for patients with chronic fatigue syndrome: A randomised controlled partially blinded trial (EUHEALS)

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Background: Distant healing, a form of spiritual healing, is widely used for many conditions but little is known about its effectiveness. Methods: In order to evaluate distant healing in patients with a stable chronic condition, we randomised 409 patients with chronic fatigue syndrome (CFS) from 14 private practices for environmental medicine in Germany and Austria in a two by two factorial design to immediate versus deferred (waiting for 6 months) distant healing. Half the patients were blinded and half knew their treatment allocation. Patients were treated for 6 months and allocated to groups of 3 healers from a pool of 462 healers in 21 European countries with different healing traditions. Change in Mental Health Component Summary (MHCS) score (SF-36) was the primary outcome and Physical Health Component Summary score (PHCS) the secondary outcome. Results: This trial population had very low quality of life and symptom scores at entry. There were no differences over 6 months in post-treatment MHCS scores between the treated and untreated groups. There was a non-significant outcome ($p = 0.11$) for healing with PHCS (1.11; 95% CI -0.255 to 2.473 at 6 months) and a significant effect ($p = 0.027$) for blinding; patients who were unblinded became worse during the trial (-1.544; 95% CI -2.913 to -0.176). We found no relevant interaction for blinding among treated patients in MHCS and PHCS. Expectation of treatment and duration of CFS added significantly to the model. Conclusions: In patients with CFS, distant healing appears to have no statistically significant effect on mental and physical health but the expectation of improvement did improve outcome. Copyright © 2008 S. Karger AG.

Thomas M.A., Sadlier M.J., Smith A.P.

A multiconvergent approach to the rehabilitation of patients with chronic fatigue syndrome: a comparative study

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Objectives: This study investigated the efficacy of a rehabilitation technique for the treatment of chronic fatigue syndrome that was developed by a physiotherapist. Data collected retrospectively from a pilot study indicated that patients benefited from this multiconvergent approach, so further assessments were warranted. Design: Treatment efficacy was assessed by comparing the primary and secondary outcome measures of patients attending multiconvergent therapy (MCT) with those of patients attending relaxation therapy and a group of non-intervention controls. Setting: The active treatment took place at a clinic within the physiotherapy outpatient unit. Relaxation therapy and all assessments were conducted at the psychology unit. Participants: Thirty-five participants,

fitting the Centers for Disease Control and Prevention criteria for chronic fatigue syndrome, were recruited from two outpatient clinics and an existing patient panel. Intervention: Patients were assigned to either MCT (n = 12) or relaxation therapy (n = 14). Nine participants who received general medical care were used as a comparison group. Main outcome measures: The Karnofsky performance scale was used as the primary outcome measure of function. Secondary outcome measures assessing overall improvement in patient condition, fatigue and disability levels were also administered. Results: A significant percentage of the patients attending the MCT sessions showed improvement in the primary outcome score used to measure the success of the treatment (MCT = 83%, relaxation = 21%, controls = 0; P < 0.001). A significant percentage of this group also reported improvement in their overall condition (MCT = 92%, relaxation = 64%, controls = 22%; P < 0.001), lower fatigue levels (MCT = 83%, relaxation = 57%, controls = 11%; P < 0.001) and lower levels of disability (MCT = 75%, relaxation = 43%, controls = 11%; P = 0.032) immediately post-therapy. In addition, these improvements were maintained at 6-month follow-up. Conclusions: Outcomes from this small preliminary study were encouraging. The multiconvergent approach produced significant improvements for standardised primary and secondary outcome measures. Further research is required to examine the efficacy of this approach over time, and its effectiveness on a larger scale within the primary healthcare setting using additional therapists trained in the technique. © 2007 Chartered Society of Physiotherapy.

Tanaka M., Fukuda S., Kei M., Imai-Matsumura K., Jodoi T., Kawatani J., Takano M., Miike T., Tomoda A., Watanabe Y.

Reliability and validity of the Japanese version of the Chalder fatigue scale among youth in Japan

2008 Psychological Reports 103 (3); 682 - 690

<http://www.scopus.com/inward/record.url?eid=2-s2.0-60749086027&partnerID=40>

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In the present study, the reliability and construct validity of the Japanese version of the Chalder Fatigue Scale was evaluated as a measure of severity of fatigue among young students in Japan. A healthy group comprised 27 Grade 6 primary school students and 28 Grade 1 junior high school students. The severely fatigued group were hospital outpatients with childhood chronic fatigue syndrome (n = 21). Principal components analysis with varimax rotation identified 4 factors which accounted for 63.2% of the total variance, as in the original English version. Internal consistency (Cronbach coefficient \hat{I}_{\pm}) was .73, and test-retest reliability measured using Spearman rank correlation coefficient was .55. Scale scores of the healthy subjects were lower than those of the patients with childhood chronic fatigue syndrome. The reliability (a) and construct validity of the Japanese version of the scale among healthy students in Japan were satisfactory for research studies among healthy school students. © Psychological Reports 2008.

Swoboda D.A.

Negotiating the diagnostic uncertainty of contested illnesses: Physician practices and paradigms

2008 Health 12 (4); 453 – 478

<http://www.scopus.com/inward/record.url?eid=2-s2.0-52649142788&partnerID=40>

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In the absence of scientific consensus about contested illnesses such as Chronic Fatigue Syndrome (CFS), Multiple Chemical Sensitivities (MCS), and Gulf War Syndrome (GWS), physicians must make sense of competing accounts and develop practices for patient evaluation. A survey of 800 United States physicians examined physician propensity to diagnose CFS, MCS, and GWS, and the factors shaping clinical decision making. Results indicate that a substantial portion of physicians, including nonexperts, are diagnosing CFS, MCS, and GWS. Diagnosing physicians manage the uncertainty associated with these illnesses by using strategies that enhance bounded rationality and aid in thinking beyond current disease models. Strategies include consulting ancillary information sources, conducting analytically informed testing, and considering physiological explanations of causation. By relying on these practices and paradigms, physicians fit CFS, MCS, and GWS into an explanatory system that makes them credible and understandable to them, their patients, and the medical community. Findings suggest that physicians employ rational decision making for diagnosing contested illnesses, creating a blueprint of how illnesses lacking conclusive pathogenic and etiological explanations can be diagnosed. Findings also suggest that patients with contested illnesses might benefit from working with physicians who use these diagnostic strategies, since they help manage the complexity and ambiguity of the contested illness diagnostic process and aid in diagnosis. In addition, findings provide a window into how emerging illnesses get diagnosed in the absence of medical and scientific consensus, and suggest that diagnosing physicians advance the legitimacy of controversial illnesses by constructing the means for their diagnosis. Copyright © 2008 SAGE Publications.

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Cognitive-behavioural therapy v. mirtazapine for chronic fatigue and neurasthenia: Randomised placebo-controlled trial

2008 British Journal of Psychiatry 192 (3); 217 – 223

<http://www.scopus.com/inward/record.url?eid=2-s2.0-40449094227&partnerID=40>

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Background: Single interventions in chronic fatigue syndrome have shown only limited effectiveness, with few studies of comprehensive treatment programmes. Aims: To examine the effect of a comprehensive cognitive-behavioural treatment (CCBT) programme compared with placebo-controlled mirtazapine medication in patients with chronic fatigue, and to study the effect of combined medication and CCBT. Method: A three-armed randomised clinical trial of mirtazapine, placebo and a CCBT programme was conducted to investigate treatment effect in a patient group (n=72) with chronic fatigue referred to a specialist clinic. The CCBT programme was compared with mirtazapine or placebo therapy for 12 weeks, followed by 12 weeks treatment with a mixed crossover-combination design. Assessments were done at 12 weeks and 24 weeks. Results: By 12 weeks the treatment effect was significantly better in the group initially receiving CCBT, as assessed with the Fatigue Scale (P=0.014) and the Clinical Global Impression Scale (P=0.001). By 24 weeks the treatment group initially receiving CCBT for 12 weeks followed by mirtazapine for 12 weeks showed significant improvement compared with the other treatment groups on the Fatigue Scale (P<0.001) and the Clinical Global impression Scale (P=0.002). Secondary outcome measures

showed overall improvement with no significant difference between treatment groups. Conclusions: Multimodal interventions may have positive treatment effects in chronic fatigue syndrome. Sequence of interventions seem to be of importance.

Scheeres K., Wensing M., Severens H., Adang E., Bleijenberg G.
Determinants of health care use in chronic fatigue syndrome patients: A cross-sectional study

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Background: Chronic fatigue syndrome (CFS) is associated with a high use of health care services. To reduce the related costs for patients and society, it will be useful to know which factors determine CFS patients' amount of health care use. Little is known, however, about these factors. Method: The present study retrospectively performed a cross-sectional analysis to investigate the possible factors determining CFS patients' health care use. A total of 263 CFS patients, derived from two subgroups (149 from tertiary care and 114 from primary/secondary care), participated. Health care use was measured with a questionnaire asking details on consumption over the past 6 months. Fatigue severity and physical functioning were measured with the subscale Experienced Fatigue of the Checklist Individual Strength (CIS-20) and the subscale Physical Functioning of the SF-36, respectively. Multiple regression analysis, T-tests, and χ^2 tests were performed. Results: The regression analysis revealed that, after controlling for patient characteristics (explaining 13%), fatigue factors added 4% predictive value and certain perpetuating factors of fatigue, including focus on bodily symptoms and attributions of fatigue, added another 5%. The analysis of subgroups revealed that, compared to the tertiary care population, fewer patients from primary/secondary care had visited a medical specialist (50% vs. 71%), used antidepressants (16% vs. 25%) and tranquilizers (3% vs. 18%), and had spent a night in hospital (7% vs. 10%). However, overall costs of health care between these subgroups did not differ. Conclusions: This study showed that illness duration, physical impairment due to fatigue, and psychological perpetuating factors of fatigue do determine the variance in CFS patients' health care use. These results give clear directions for treating CFS patients and managing health care for CFS. © 2008 Elsevier Inc. All rights reserved.

Scheeres K., Wensing M., Knoop H., Bleijenberg G.
Implementing Cognitive Behavioral Therapy for Chronic Fatigue Syndrome in a Mental Health Center: A Benchmarking Evaluation

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-38949097814&partnerID=40>

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Objective: This study evaluated the success of implementing cognitive behavioral therapy (CBT) for chronic fatigue syndrome (CFS) in a representative clinical practice setting and compared the patient outcomes with those of previously published randomized controlled trials (RCTs) of CBT for CFS. Method: The implementation interventions were the following: spreading information about the new treatment setting to general practitioners and CFS patients; training mental health center (MHC) therapists in CBT for CFS; and organizing changes in the MHC patient workflow. Patient outcomes were documented with validated self-report measures of fatigue and physical functioning before and after treatment. The comparison of the treatment results with RCT results was done following the benchmark strategy. Results: One-hundred forty-three CFS patients were referred to the MHC, of

whom 112 started treatment. The implementation was largely successful, but a weak point was the fact that 32% of all referred patients dropped out shortly after or even before starting treatment. Treatment effect sizes were in the range of those found in the benchmark studies. Conclusions: CBT for CFS can successfully be implemented in an MHC. Treatment results were acceptable, but the relatively large early dropout of patients needs attention. © 2008 American Psychological Association.

Scheeres K., Wensing M., Bleijenberg G., Severens J.L.

Implementing cognitive behavior therapy for chronic fatigue syndrome in mental health care: A costs and outcomes analysis

2008 BMC Health Services Research 8

<http://www.scopus.com/inward/record.url?eid=2-s2.0-51849093602&partnerID=40>

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Background. This study investigated the costs and outcomes of implementing cognitive behavior therapy (CBT) for chronic fatigue syndrome (CFS) in a mental health center (MHC). CBT is an evidence-based treatment for CFS that was scarcely available until now. To investigate the possibilities for wider implementation, a pilot implementation project was set up. **Method.** Costs and effects were evaluated in a non-controlled before- and after study with an eight months time-horizon. Both the costs of performing the treatments and the costs of implementing the treatment program were included in the analysis. The implementation interventions included: informing general practitioners (GPs) and CFS patients, training therapists, and instructing the MHC employees. Given the non-controlled design, cost outcome ratios (CORs) and their acceptability curves were analyzed. Analyses were done from a health care perspective and from a societal perspective. Bootstrap analyses were performed to estimate the uncertainty around the cost and outcome results. **Results.** 125 CFS patients were included in the study. After treatment 37% had recovered from CFS and the mean gained QALY was 0.03. Costs of patients' health care and productivity losses had decreased significantly. From the societal perspective the implementation led to cost savings and to higher health states for patients, indicating dominance. From the health care perspective the implementation revealed overall costs of €5,320 per recovered patient, with an acceptability curve showing a 100% probability for a positive COR at a willingness to pay threshold of €6,500 per recovered patient. **Conclusion.** Implementing CBT for CFS in a MHC appeared to have a favorable cost outcome ratio (COR) from a societal perspective. From a health care perspective the COR depended on how much a recovered CFS patient is being valued. The strength of the evidence was limited by the non-controlled design. The outcomes of this study might facilitate health care providers when confronted with the decision whether or not to adopt CBT for CFS in their institution. © 2008 Scheeres et al; licensee BioMed Central Ltd.

Reynolds F., Vivat B., Prior S.

Women's experiences of increasing subjective well-being in CFS/ME through leisure-based arts and crafts activities: A qualitative study

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-53249105449&partnerID=40>

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Purpose. To understand the meanings of art-making among a group of women living with the occupational constraints and stigma of CFS/ME. The study explored their initial motives for art-making, and then examined how art-making had subsequently influenced their subjective well-

being. Method. Ten women with CFS/ME were interviewed; three provided lengthy written accounts to the interview questions. Findings. Illness had resulted in devastating occupational and role loss. Participants took many years to make positive lifestyle changes. Art-making was typically discovered once participants had accepted the long-term nature of CFS/ME, accommodated to illness, and reprioritized occupations. Several factors then attracted participants specifically to art-making. It was perceived as manageable within the constraints of ill-health. Participants also tended to be familiar with craft skills; had family members interested in arts and crafts, and some desired a means to express grief and loss. Once established as a leisure activity, art-making increased subjective well-being mainly through providing increased satisfaction in daily life, positive self-image, hope, and contact with the outside world. Participants recommended provision of occupational/recreational counselling earlier in the illness trajectory. Conclusions. Creative art-making occurred as part of a broader acceptance and adjustment process to CFS/ME, and allowed some psychological escape from a circumscribed lifeworld.

Nunez M., Nunez E., Del Val J.L., Fernandez-Huerta J.M., Alegre C., Bonet M., Roig D., Gomez E., Godas Sieso T., Fernandez-Sola J.
Health-related quality of life in chronic fatigue syndrome versus rheumatoid arthritis as control group

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-39049115892&partnerID=40>

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The objectives of this study were (1) evaluate health-related quality of life (HRQL) in patients with chronic fatigue syndrome (CFS); (2) to compare the HRQL of these patients with that of rheumatoid arthritis (RA) patients and healthy Spanish reference population values (RPV); and (3) to identify the influence of sociodemographic and clinical variables on HRQL in CFS patients. We included 216 outpatients: 94 females/14 males (age 42.9 \pm 9.9 years) with CFS and 94 females/14 males with RA (age 42.9 \pm 9.9 years). We used a cross-sectional, observational design. Sociodemographic data, comorbidities, pain (VAS) and global functional status were determined. HRQL was measured by the SF-36 and HAQ questionnaires. CFS patients had worse scores than RA patients in all SF36 dimensions except emotional role ($p < 0.01$). Both CFS and RA patients had worse scores in all SF36 dimensions than RPV. In CFS patients, pain negatively influenced HRQL ($p < 0.05$) except for physical role, social function and emotional role. Global functional status negatively influenced HRQL ($p < 0.05$) except for bodily pain, general health and mental health. Comorbidities worsened scores for physical and social functions and mental health. In conclusion, HRQL was worse in patients with CFS than in those with RA. Both CFS and RA patients had worse HRQL compared with RPV. Comorbidities, pain and global functional status influenced HRQL in CFS patients. Standardised HRQL instruments are of value in determining the quality of life in these patients. Copyright    by The Haworth Press, Inc. All rights reserved.

Nijs J., Thielemans A.

Kinesiophobia and symptomatology in chronic fatigue syndrome: A psychometric study of two questionnaires

2008 *Psychology and Psychotherapy: Theory, Research and Practice* 81 (3); 273 – 283

<http://www.scopus.com/inward/record.url?eid=2-s2.0-50849090939&partnerID=40>

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Objectives: The aims of the study were to examine the reliability of the Dutch and French versions of the Tampa scale kinesiophobia (TSK) version chronic fatigue syndrome (CFS), and to examine the reliability and validity of the Dutch and French versions of the CPS symptom list. **Design.** Repeated-measures design. **Methods.** Native Dutch speakers (N = 100) and native French (N = 48) speakers fulfilling the diagnostic criteria for CFS were asked to list the five most important symptoms and to complete the TSK-CFS, the CFS symptom list, and the Short Form 36 Health Status Survey or SF-36. A modified version of the TSK-CFS and the CFS symptom list was filled in within 24 hours of the first assessment. **Results.** The French and Dutch version of the TSK-CFS and CFS symptom lists displayed good reliability (ICC \geq .83). The CFS symptom list was internally consistent (Cronbach's α = .93) and concurrently valid with the SF-36. For the native Dutch and French speakers, respectively, 82 and 78% of the self-reported symptoms matched the content of CFS symptom list. **Conclusions.** The results are in support of the psychometric properties of the French and Dutch versions of both the TSK-CFS and the CFS symptom list for assessing kinesiophobia and symptom severity, respectively. © 2008 The British Psychological Society.

Nijs J., Paul L., Wallman K.

Chronic fatigue syndrome: An approach combining self-management with graded exercise to avoid exacerbations

2008 *Journal of Rehabilitation Medicine* 40 (4); 241 – 247

<http://www.scopus.com/inward/record.url?eid=2-s2.0-42649135188&partnerID=40>

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Controversy regarding the aetiology and treatment of patients with chronic fatigue syndrome continues among the medical professions. The Cochrane Collaboration advises practitioners to implement graded exercise therapy for patients with chronic fatigue syndrome using cognitive behavioural principles. Conversely, there is evidence that exercise can exacerbate symptoms in chronic fatigue syndrome, if too-vigorous exercise/activity promotes immune dysfunction, which in turn increases symptoms. When designing and implementing an exercise programme for chronic fatigue syndrome it is important to be aware of both of these seemingly opposing viewpoints in order to deliver a programme with no detrimental effects on the pathophysiology of the condition. Using evidence from both the biological and clinical sciences, this paper explains that graded exercise therapy for people with chronic fatigue syndrome can be undertaken safely with no detrimental effects on the immune system. Exercise programmes should be designed to cater for individual physical capabilities and should take into account the fluctuating nature of symptoms. In line with cognitive behaviourally and graded exercise-based strategies, self-management for people with chronic fatigue syndrome involves encouraging patients to pace their activities and respect their physical and mental limitations, with the ultimate aim of improving their everyday functioning. © 2008 Foundation of Rehabilitation Information.

Nijs J., Almond F., de Becker P., Truijen S., Paul L.
Can exercise limits prevent post-exertional malaise in chronic fatigue syndrome? An uncontrolled clinical trial

2008 *Clinical Rehabilitation* 22 (5); 426 - 435

<http://www.scopus.com/inward/record.url?eid=2-s2.0-45149097742&partnerID=40>

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Objective: It was hypothesized that the use of exercise limits prevents symptom increases and worsening of their health status following a walking exercise in people with chronic fatigue syndrome. **Design:** An uncontrolled clinical trial (semi-experimental design). **Setting:** Outpatient clinic of a university department. **Subjects:** Twenty-four patients with chronic fatigue syndrome. **Interventions:** Subjects undertook a walking test with the two concurrent exercise limits. Each subject walked at an intensity where the maximum heart rate was determined by heart rate corresponding to the respiratory exchange ratio = 1.0 derived from a previous submaximal exercise test and for a duration calculated from how long each patient felt they were able to walk. **Main outcome measures:** The Short Form 36 Health Survey or SF-36, the Chronic Fatigue Syndrome Symptom List, and the Chronic Fatigue Syndrome - Activities and Participation Questionnaire were filled in prior to, immediately after and 24 hours after exercise. **Results:** The fatigue increase observed immediately post-exercise ($P=0.006$) returned to pre-exercise levels 24 hours post-exercise. The increase in pain observed immediately post-exercise was retained at 24 hours post-exercise ($P=0.03$). Fourteen of the 24 subjects experienced a clinically meaningful change in bodily pain (change of SF-36 bodily pain score ≥ 10); 6 indicated that the exercise bout had slightly worsened their health status, and 2 had a clinically meaningful decrease in vitality (change of SF-36 vitality score ≥ 20). There was no change in activity limitations/participation restrictions. **Conclusion:** It was shown that the use of exercise limits (limiting both the intensity and duration of exercise) prevents important health status changes following a walking exercise in people with chronic fatigue syndrome, but was unable to prevent short-term symptom increases. © SAGE Publications 2008.

Malaguarnera M., Gargante M.P., Cristaldi E., Colonna V., Messano M., Koverech A., Neri S., Vacante M., Cammalleri L., Motta M.

Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-38949140508&partnerID=40>

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Fatigue is one of the conditions most frequently complained by the elderly. There are few effective treatment options for patients with chronic fatigue syndrome. To determine the efficacy, tolerability and impact on the fatigue, as well as on cognitive and functional status of elderly subjects with acetyl L-carnitine (ALC), 96 aged subjects (>70 years, range 71-88) were investigated (50 females and 46 males; mean age 76.2 ± 7.6 and 78.4 ± 6.4 years, respectively). They met four or more of the Holmes major criteria or at least six of Fukuda minor criteria. Fatigue was measured with the Wessely and Powell [Wessely, S., Powell, R., 1989. Fatigue syndromes: a comparison of chronic postviral fatigue with neuromuscular and affective disorders. *J. Neurol. Neurosurg. Psychiatry* 52,

940-948] scores, with the fatigue severity scale. At the end of the treatment, we observed a decrease of physical fatigue: 6.2 ($p < 0.001$), of mental fatigue: 2.8 ($p < 0.001$), of severity fatigue: 21.0 ($p < 0.001$) and improvements in functional status: 16.1 ($p < 0.001$) and cognitive functions: 2.7 ($p < 0.001$). By the end of the treatment, significant differences between the two groups were found for the following parameters: muscle pain -27% versus -3% ($p < 0.05$); prolonged fatigue after exercise: 51% versus -4% ($p < 0.0001$); sleep disorders: 28% versus 4% ($p < 0.05$); physical fatigue: 7 versus -0.5 ($p < 0.0001$); mental fatigue: -3.3 versus 0.6 ($p < 0.0001$); fatigue severity scale: -22.5 versus 1.2 ($p < 0.0001$); functional status 17.1 versus 0.6 ($p < 0.0001$); mini mental state examination (MMSE) improvements: 3.4 versus 0.5 ($p < 0.0001$). Our data show that administering ALC may reduce both physical and mental fatigue in elderly and improves both the cognitive status and physical functions. © 2007.

Lu T.V., Torres-Harding S.R., Jason L.A.

The effectiveness of early educational intervention in improving future physicians' attitudes regarding CFS/FM

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-39049095003&partnerID=40>

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Objective: To assess the effects of an early educational intervention program's ability to alter the perceptions and attitudes of future physicians regarding chronic fatigue syndrome/fibromyalgia (CFS/FM), improve their understanding and acceptance of these diseases, make them feel more comfortable in diagnosing and treating patients. Method: Third-year medical students were surveyed before and after an educational intervention program. The three questions posed to the students in the survey were: (1) How comfortable do you feel you are in diagnosing and treating patients with CFS /FM?, (2) Do you consider CFS/FM legitimate illnesses?, and (3) Do you want to treat patients with CFS/FM? Results: The educational intervention program helped about half of the future physicians feel comfortable in diagnosing and treating patients with CFS/FM and improved by over 25% their willingness to treat patients with CFS. Conclusion: An educational intervention program appeared to improve future physicians' understanding and appreciation of CFS/FM, made them feel more comfortable diagnosing and treating these diseases, and increased their willingness to treat patients with CFS/FM. Copyright © by The Haworth Press, Inc. All rights reserved.

Lowry T.J., Pakenham K.I.

Health-related quality of life in chronic fatigue syndrome: Predictors of physical functioning and psychological distress

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This study investigated health-related quality of life (HRQoL; physical functioning and psychological distress) in an Australian chronic fatigue syndrome (CFS) population. The aims of the study were to compare HRQoL in those with CFS to the normal population, and to investigate the extent to which sociodemographic (age, gender, partner status, education), illness-related (illness duration, symptom frequency), and fatigue severity (physical, mental) variables predicted HRQoL. A total of 139 people meeting CFS criteria completed questionnaires. HRQoL was assessed using standardised measures of distress and physical functioning. Compared with norms, those with CFS obtained significantly lower scores on all physical functioning areas, whereas 63% of participants reported

clinically significant psychological distress. Hierarchical regression analyses indicated that physical fatigue severity and symptom frequency were the strongest predictors of deficits in physical domain HRQoL. Physical HRQoL outcomes were also predicted by mental fatigue severity, older age, and female gender. All predictors were unrelated to psychological distress apart from weak positive associations with physical fatigue and symptom frequency. Results identify a potent set of predictors of HRQoL and show that CFS has a pervasive negative impact on quality of life, particularly physical and psychological functioning. © 2008 Taylor & Francis.

Lerner A.M., Beqaj S.H., Fitzgerald J.T.

Validation of the energy index point score to serially measure the degree of disability in patients with chronic fatigue syndrome

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Background: A simple quantitative accurate method for assessing the degree of fatigue in patients with chronic fatigue syndrome (CFS) is necessary for physicians and patients. Severity of the disease and recovery can, thus, be assayed. Patient and Methods: From February 1-27, 2007, fifty-six consecutive CFS patients at a single treatment center were simultaneously evaluated by the patient with the fatigue severity score (FSS), and by consensus of both patient and physician by the energy index (EI) point score. Results: The FSS and EI correlated well, 0.67, $p < 0.001$. Conclusion: The EI point score is a validated reliable method to assess fatigue in CFS patients.

Kumar A., Garg R., Kumar P.

Nitric oxide modulation mediates the protective effect of trazodone in a mouse model of chronic fatigue syndrome

2008 Pharmacological Reports 60 (5); 664 – 672

<http://www.scopus.com/inward/record.url?eid=2-s2.0-57849120104&partnerID=40>

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The present study was conducted with the aim of elucidating the possible role of nitric oxide (NO) in the neuroprotective effects of trazodone used to treat chronic fatigue syndrome (CFS) in mice. Male albino mice were forced to swim for a six minute session each day for 7 days and the immobility period was recorded every other day. Trazodone (5 mg/kg and 10 mg/kg) was administered each day 30 min before the forced swim test. In addition, L-arginine (100 mg/kg) and L-NAME (5 mg/kg) were administered 15 min before administration of trazodone (5 mg/kg). Various behavioral tests, including locomotor (actophotometer) and anxiety (mirror chamber and plus maze) tests, as well as biochemical parameters (lipid peroxidation, reduced glutathione, catalase, and nitrites) were evaluated on the 8th day. Forced swimming for 7 days caused a chronic fatigue-like condition, anxiety-like behavior, impairments in locomotor activity, and oxidative damage (increased lipid peroxidation and nitrite levels, and depletions in the reduced forms of glutathione and catalase activity) in animals. Pretreatment with L-NAME (5 mg/kg) potentiated the antioxidant effect of trazodone (5 mg/kg). However, L-arginine (100 mg/kg) pretreatment reversed the protective effect of trazodone (5 mg/kg) ($p < 0.05$). The present study suggests the possible involvement of NO signaling in the protective effect of trazodone. Copyright © 2008 by Institute of Pharmacology Polish Academy of Sciences.

Knoop H., Van Der Meer J.W.M., Bleijenberg G.

Guided self-instructions for people with chronic fatigue syndrome: Randomised controlled trial

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A minimal intervention, based on cognitive-behavioural therapy for chronic fatigue syndrome and consisting of selfinstructions combined with email contact, was tested in a randomised controlled trial (ISRCTN27293439). A total of 171 patients participated in the trial: 85 were allocated to the intervention condition and 86 to the waiting-list condition. All patients met the Centers for Disease Control and Prevention criteria for chronic fatigue syndrome. An intention-to-treat analysis showed a significant decrease in fatigue and disability after self-instruction. The level of disability was negatively correlated with treatment outcome. Guided selfinstructions are an effective treatment for patients with relatively less severe chronic fatigue syndrome.

Knoop H., Stulemeijer M., De Jong L.W.A.M., Fiselier T.J.W., Bleijenberg G.

Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: Long-term follow of a randomized, controlled trial

2008 Pediatrics 121 (3)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-40949089743&partnerID=40>

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Objectives.The purpose of this work was to assess the long-term outcome of adolescents with chronic fatigue syndrome who received cognitive behavioral therapy and to determine the predictive value of fatigue severity and physical impairments of the adolescent and the fatigue severity of the mother at baseline for the outcome of the treatment at follow-up. **Patients And Methods.** Sixty-six adolescent patients with chronic fatigue syndrome who previously participated in a randomized, controlled trial that showed that cognitive behavioral therapy was more effective than a waiting-list condition in reducing fatigue and improving physical functioning were contacted for a follow-up assessment. Fifty participants of the follow-up study had received cognitive behavioral therapy for chronic fatigue syndrome (32 formed the cognitive behavioral therapy group in the original trial, and 18 patients received cognitive behavioral therapy after the waiting period). The remaining 16 patients had refused cognitive behavioral therapy after the waiting period. The main outcome measures were fatigue severity (Checklist Individual Strength), physical functioning (Short-Form General Health Survey), and school attendance. **Results.**Data were complete for 61 patients at follow-up (cognitive behavioral therapy group: 47 patients; no-treatment group: 14 patients). The mean follow-up time was 2.1 years. There was no significant change in fatigue severity between posttreatment and follow-up in the cognitive behavioral therapy group. There was a significant further increase in physical functioning and school attendance (10% increase). The adolescents in the cognitive behavioral therapy group were significantly less fatigued and significantly less functionally impaired and had higher school attendance at follow-up than those in the no-treatment group. Fatigue severity of the mother was a significant predictor of treatment outcome. **Conclusions.** The positive effects of cognitive behavioral therapy in adolescents with chronic fatigue syndrome are sustained after cognitive behavioral therapy. Higher fatigue severity of the mother predicts lower treatment outcome in adolescent patients. Copyright © 2008 by the American Academy of Pediatrics.

Kelly M., Gagne R., Newman J.D., Olney C., Gualtieri C., Trail D.
Assessment of fibromyalgia & chronic fatigue syndrome: a new protocol designed to determine work capability--chronic pain abilities determination (CPAD).

2008 Irish medical journal 101 (9); 277 - 278

<http://www.scopus.com/inward/record.url?eid=2-s2.0-58149377028&partnerID=40>

The objective was to design a protocol to assess work ability in people suffering ill-defined painful and disabling disorders, the outstanding prototype of which is fibromyalgia/chronic fatigue syndrome (FM/CSF). Following an extensive literature search, the most appropriate components of current methods of assessment of physical and cognitive abilities were incorporated into the protocol, occasionally with appropriate modification to suit the specific requirements of the individual. The initial part of the assessment consists of a standard history taking, principally focusing on the patient's self-reported physical and cognitive abilities and disabilities, as well as the completion of established pain and fatigue scales, and relevant disability questionnaires. Following this, physical and cognitive abilities are objectively assessed on two separate occasions, utilizing computerized hand-held dynamometers, inclinometers, algometers, and force dynamometers. Specific work simulation tests using the industrial standards Methods-Time-Measurement testing are avoided, as is aerobic testing using the Canadian Aerobic Fitness Test (CAFT). Objective computerised neuro-cognitive testing are also utilised as an integral component of the assessment. All results are then subject to specific computerized analysis and compared to normative and standardised work-based databases. The designed system produces reliable, consistent and reproducible results. It also proves capable of detecting any inconsistencies in patient input and results, in addition to being independent of any possible assessor bias. A new protocol has been designed to determine the working capability of individuals who suffer from various chronic disabling conditions, and represents a significant step forward in a difficult but rapidly expanding area of medical practice.

Johnson S.K., Gil-Rivas V., Schmalzing K.B.

Coping strategies in chronic fatigue syndrome: Outcomes over time

2008 Stress and Health 24 (4); 305 - 312

<http://www.scopus.com/inward/record.url?eid=2-s2.0-56749155310&partnerID=40>

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This paper examined the contribution of coping strategies and neuroticism to longitudinal outcomes in a tertiary care sample of participants with chronic fatigue syndrome (CFS). Coping strategies and neuroticism were assessed among 93 participants with CFS, and used to predict participants' illness-related outcomes. Coping by instrumental support was the only strategy associated with clinical outcomes over time: more reliance on instrumental support predicted less vitality over time after accounting for the level of vitality at the index visit. Neuroticism and coping strategies were not associated with fatigue symptoms, physical functioning or role functioning over time. Copyright © 2008 John Wiley & Sons, Ltd.

Jason L., Muldowney K., Torres-Harding S.

The Energy Envelope Theory and myalgic encephalomyelitis/chronic fatigue syndrome.

2008 AAOHN journal : official journal of the American Association of Occupational Health Nurses 56 (5); 189 - 195

<http://www.scopus.com/inward/record.url?eid=2-s2.0-51149083504&partnerID=40>

DePaul University, Chicago, IL, USA.

Individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) have little stamina and endurance, and pose a challenge for nursing professionals. The Energy Envelope Theory, which

posits that maintaining expended energy levels consistent with available energy levels may reduce the frequency and severity of symptoms, is particularly useful when working with clients with ME/CFS. Anecdotal support from the client community for this theory supports its use as a management tool for ME/CFS, but little formal research has been done in this area. In this study, a daily energy quotient was established by dividing the expended energy level by the perceived energy level and multiplying by 100. It was predicted that those participants who expended energy beyond their level of perceived energy would have more severe fatigue and symptoms and lower levels of physical and mental functioning. Findings are congruent with the Energy Envelope Theory as they indicated that the daily energy quotient was related to several indices of functioning including depression, anxiety, fatigue, pain, quality of life, and disability. The overall results provide support for a strategy health care professionals can use when working with clients with ME/CFS.

Huang Y., Liao X.-M., Li X.-X., Song Y.-B.

Clinical observation on the effects of Bo's abdominal acupuncture in 40 cases of chronic fatigue syndrome

2008 Journal of Traditional Chinese Medicine 28 (4); 264 – 266

<http://www.scopus.com/inward/record.url?eid=2-s2.0-59149092705&partnerID=40>

Southern Medical University, Guangzhou 510515, China

Objective: To observe the curative effect of Bo's abdominal acupuncture on chronic fatigue syndrome (CFS). Methods: Forty cases with CFS were treated by Bo's abdominal acupuncture at the points for conducting qi back to its origin and 4 points on the abdomen once a day for 2 weeks. Scores for symptoms and scores for fatigue questionnaires were compared before and after treatment. Results: After treatment, the clinical symptoms of patients were differently alleviated, and scores for symptoms, mental condition and neural feeling in questionnaires on fatigue were obviously reduced ($P < 0.01-0.05$). Conclusion: Bo's abdominal acupuncture has a good curative effect on general di ease with complex symptoms, especially on lassitude, anorexia, insomnia, amnesia, diarrhea, and general pain.

Hobday R.A., Thomas S., O'donovan A., Murphy M., Pinching A.J.

Dietary intervention in chronic fatigue syndrome

2008 Journal of Human Nutrition and Dietetics 21 (2); 141 – 149

<http://www.scopus.com/inward/record.url?eid=2-s2.0-40949129239&partnerID=40>

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Background: Anecdotal reports and books have been published linking an over growth of *Candida Albicans* with chronic fatigue syndrome (CFS), suggesting dietary change as a treatment option. Little scientific data has been published to validate this controversial theory. This study aims to determine the efficacy of dietary intervention on level of fatigue and quality of life (QoL) in individuals with CFS. Methods: A 24-week randomized intervention study was conducted with 52 individuals diagnosed with CFS. Patients were randomized to either a low sugar low yeast (LSLY) or healthy eating (HE) dietary interventions. Primary outcome measures were fatigue as measured by the Chalder Fatigue Score and QoL measured by Medical Outcomes Survey Short Form-36. Results: A high drop out rate occurred with 13 participants not completing the final evaluation (7HE/6LSLY). Intention to treat analysis showed no statistically significant differences on primary outcome measurements. Conclusion: In this randomized control trial, a LSLY diet appeared to be no more efficacious on levels of fatigue or QoL compared to HE. Given the difficulty with dietary compliance experienced by participants, especially in the LSLY group, it would appear HE guidance is a more pragmatic approach than advocating a complicated dietary regime. © 2008 The British Dietetic Association.

Gilje A.M., Soderlund A., Malterud K.

Obstructions for quality care experienced by patients with chronic fatigue syndrome (CFS)-A case study

2008 Patient Education and Counseling 73 (1); 36 – 41

<http://www.scopus.com/inward/record.url?eid=2-s2.0-50549100410&partnerID=40>

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Objective: To explore obstructions for quality care from experiences by patients suffering from chronic fatigue syndrome (CFS). Methods: Qualitative case study with data drawn from a group meeting, written answers to a questionnaire and a follow-up meeting. Purposeful sample of 10 women and 2 men of various ages, recruited from a local patient organization, assumed to have a special awareness for quality care. Results: CFS patients said that lack of acknowledgement could be even worse than the symptoms. They wanted their doctors to ask questions, listen to them and take them seriously, instead of behaving degrading. Many participants felt that the doctors psychologized too much, or trivialized the symptoms. Participants described how doctors' lack of knowledge about the condition would lead to long-term uncertainty or maltreatment. Even with doctors who were supportive, it would usually take months and sometimes years until a medical conclusion would be reached, or other disorders were ruled out. Increased physical activity had been recommend, but most of the informants experienced that this made them worse. Conclusion: Current medical scepticism and ignorance regarding CFS shapes the context of medical care and the illness experiences of CFS patients, who may feel they neither get a proper assessment nor management. Practice implications: CFS patients' reports about patronizing attitudes and ignorance among doctors call for development of evidence based strategies and empowerment of patients, acknowledging the patients' understanding of symptoms and the complex nature of the disease. The NICE guidelines emphasize the need of patient participation and shared decision-making. © 2008 Elsevier Ireland Ltd. All rights reserved.

Friedberg F., Sohl S., Halperin P.

Teaching medical students about medically unexplained illnesses: A preliminary study

2008 Medical Teacher 30 (6); 618 - 621

<http://www.scopus.com/inward/record.url?eid=2-s2.0-48749107675&partnerID=40>

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Background: This study examined how an interactive seminar focusing on two medically unexplained illnesses, chronic fatigue syndrome (CFS) and fibromyalgia, influenced medical student attitudes toward CFS, a more strongly stigmatized illness. Methods: Forty-five fourth year medical students attended a 90 minute interactive seminar on the management of medically unexplained illnesses that was exemplified with CFS and fibromyalgia. A modified version of the CFS attitudes test was administered immediately before and after the seminar. Results: Pre-seminar assessment revealed neutral to slightly favorable toward CFS. At the end of the seminar, significantly more favorable attitudes were found toward CFS in general ($t(42) = 2.77$; $P < 0.01$) and for specific items that focused on (1) supporting more CFS research funding ($t(42) = 4.32$; $P < 0.001$); (2) employers providing flexible hours for people with CFS ($t(42) = 3.52$, $P < 0.01$); and (3) viewing CFS as not primarily a psychological disorder ($t(42) = 2.87$, $P < 0.01$). Thus, a relatively brief exposure to factual information on specific medically unexplained illnesses was associated with more favorable attitudes toward CFS in fourth year medical students. Conclusion: This type of instruction may lead to potentially more receptive professional attitudes toward providing care to these underserved patients.

Dhir A., Kulkarni S.K.

Venlafaxine reverses chronic fatigue-induced behavioral, biochemical and neurochemical alterations in mice

2008 Pharmacology Biochemistry and Behavior 89 (4); 563 – 571

<http://www.scopus.com/inward/record.url?eid=2-s2.0-41949128168&partnerID=40>

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A state of chronic fatigue was produced in mice by subjecting them to forced swim inside a rectangular jar of specific dimensions everyday for a 6Å min session for 15Å days. Immobility period was recorded on alternate days. The effect of venlafaxine, a dual reuptake inhibitor of serotonin and norepinephrine was evaluated in this murine model of chronic fatigue. Venlafaxine was administered daily and on the days of testing, it was injected 30Å min before forced swim session. On the 16th day i.e. 24Å h after the last dose of venlafaxine, various behavioral, biochemical and neurotransmitter estimations in the brain were carried out. There was a significant increase in immobility period in vehicle treated mice on successive days, the maximum immobility score reaching on the 7th day and sustained till 15th day. Behavioral parameters revealed hyperlocomotion, anxiety response, muscle incoordination, hyperalgesia and memory deficit. Biochemical analysis showed a significant increase in lipid peroxidation, nitrite and myeloperoxidase levels and a decrease in the reduced glutathione (GSH) levels in brain homogenates. Further, there was a decrease in adrenal ascorbic acid following chronic forced swim. The neurotransmitter estimations in the brain samples revealed a decrease in norepinephrine, serotonin and dopamine levels on chronic exposure to forced swim for 15Å days. Daily treatment with venlafaxine (8 and 16Å mg/kg, i.p.) for 15Å days produced a significant reduction in immobility period and reversed various behavioral, biochemical and neurotransmitter alterations induced by chronic fatigue. Venlafaxine could be of therapeutic potential in the treatment of chronic fatigue. Å© 2008 Elsevier Inc. All rights reserved.

De Lange F.P., Koers A., Kalkman J.S., Bleijenberg G., Hagoort P., Van Der Meer J.W.M., Toni I.

Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome

2008 Brain 131 (8); 2172 - 2180

<http://www.scopus.com/inward/record.url?eid=2-s2.0-49549098628&partnerID=40>

F.C. Donders Centre for Cognitive Neuroimaging, Radboud University Nijmegen, Netherlands; Expert Center Chronic Fatigue, Radboud University Nijmegen Medical Center, Netherlands; Nijmegen Institute for Cognition and Information, Radboud University Nijmegen, Netherlands; Department of General Internal Medicine, Radboud University Nijmegen Medical Center, Netherlands; F.C. Donders Centre for Cognitive Neuroimaging, Radboud University Nijmegen, Kapittelweg 29, 6500 HB Nijmegen, Netherlands

Chronic fatigue syndrome (CFS) is a disabling disorder, characterized by persistent or relapsing fatigue. Recent studies have detected a decrease in cortical grey matter volume in patients with CFS, but it is unclear whether this cerebral atrophy constitutes a cause or a consequence of the disease. Cognitive behavioural therapy (CBT) is an effective behavioural intervention for CFS, which combines a rehabilitative approach of a graded increase in physical activity with a psychological approach that addresses thoughts and beliefs about CFS which may impair recovery. Here, we test the hypothesis that cerebral atrophy may be a reversible state that can ameliorate with successful CBT. We have quantified cerebral structural changes in 22 CFS patients that underwent CBT and 22 healthy control participants. At baseline, CFS patients had significantly lower grey matter volume than healthy control participants. CBT intervention led to a significant improvement in health status, physical activity and cognitive performance. Crucially, CFS patients showed a significant increase in grey matter volume, localized in the lateral prefrontal cortex. This change in cerebral volume was related to improvements in cognitive speed in the CFS patients. Our findings indicate that the

cerebral atrophy associated with CFS is partially reversed after effective CBT. This result provides an example of macroscopic cortical plasticity in the adult human brain, demonstrating a surprisingly dynamic relation between behavioural state and cerebral anatomy. Furthermore, our results reveal a possible neurobiological substrate of psychotherapeutic treatment. © The Author (2008). Published by Oxford University Press on behalf of the Guarantors of Brain. All rights reserved.

Dawes J., Stephenson M.D.
Training individuals with chronic fatigue syndrome

2008 Strength and Conditioning Journal 30 (6); 55 – 57

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67649954725&partnerID=40>

National Strength and Conditioning Association, Colorado Springs, CO

This column will focus on recommendations for developing a comprehensive strength and conditioning program for individuals with chronic fatigue syndrome. Copyright © National Strength and Conditioning Association.

Chew-Graham C.A., Cahill G., Dowrick C., Wearden A., Peters S.
Using multiple sources of knowledge to reach clinical understanding of chronic fatigue syndrome

2008 Annals of Family Medicine 6 (4); 340 – 348

<http://www.scopus.com/inward/record.url?eid=2-s2.0-48249149924&partnerID=40>

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PURPOSE: Chronic fatigue syndrome (CFS), or myalgic encephalitis (ME), is a contentious condition and often a diagnosis of exclusion. Current policy in the United Kingdom recommends management in primary care. We explored how patients with CFS/ME and family physicians understand this condition and how their understanding might affect the primary care consultation. **METHODS:** We undertook a qualitative study with patients and family physicians from North West England participating in a primary care-based randomized controlled trial (FINE Trial). Data were collected through purposive sampling and in-depth semistructured interviews with 24 patients and 14 family physicians. We analyzed interview transcripts using constant comparison methods. **RESULTS:** Family physicians access social and cultural knowledge to reach a clinical understanding of CFS/ME and its management. Patients recognize the difficulties family physicians encounter in understanding their symptoms and access similar nonclinical sources of information. We suggest that both patients and physicians use biomedical discourse within the consultation: the physician to maintain the position as an expert, the patient to engage the physician. **CONCLUSIONS:** Family physicians obtain information about CFS/ME from their nonprofessional world, which they incorporate into their professional realm. Patients and physicians describe the use of the discourse of science within consultations about CFS/ME. This form of shared understanding could lead to a positive collaborative interaction. Family physicians need a biomedical, evidence-based knowledge about CFS/ME. There is potential to use the rich knowledge base that patients can bring to consultations in training initiatives directed at family physicians.

Brimmer D.J., McCleary K.K., Lupton T.A., Faryna K.M., Hynes K., Reeves W.C.
A train-the-trainer education and promotion program: Chronic fatigue syndrome - A diagnostic and management challenge

2008 BMC Medical Education 8

<http://www.scopus.com/inward/record.url?eid=2-s2.0-55149111834&partnerID=40>

Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States; CFIDS Association of America, Charlotte, NC, United States; Illinois AHEC Program, Northwestern University, Downers Grove, IL, United States

Background. Chronic fatigue syndrome (CFS) is a complicated illness for providers and patients. Fewer than 20% of persons with CFS have been diagnosed and treated. For providers, compounding the issue are the challenges in making a diagnosis due to the lack of a biomedical marker. **Methods.** The objective of the CFS diagnosis and management curriculum was to instruct core trainers as to the evaluation, diagnosis, and management of CFS. Over a two year period, 79 primary care physicians, physician assistants, and nurse practitioners from diverse regions in the U.S. participated as core trainers in a two day Train-the-Trainer (TTT) workshop. As core trainers, the workshop participants were expected to show increases in knowledge, self-efficacy, and management skills with the primary goal of conducting secondary presentations. **Results.** The optimal goal for each core trainer to present secondary training to 50 persons in the health care field was not reached. However, the combined core trainer group successfully reached 2064 primary care providers. Eighty-two percent of core trainers responded "Very good" or "Excellent" in a post-test survey of self-efficacy expectation and CFS diagnosis. Data from the Chicago workshops showed significant improvement on the Primary Care Opinion Survey ($p < 0.01$) and on the Relevance and Responsibility Factors of the CAT survey ($p = 0.03$ and $p = 0.04$, respectively). Dallas workshop data show a significant change from pre- to post-test scores on the CFS Knowledge test ($p = 0.001$). Qualitative and process evaluation data revealed that target audience and administrative barriers impacted secondary training feasibility. **Conclusion.** Data show the workshop was successful in meeting the objectives of increasing CFS knowledge and raising perceived self-efficacy towards making a diagnosis. The CFS TTT program informed an educational provider project by shifting the format for physicians to grand rounds and continuing medical education design while retaining TTT aspects for nurse practitioners and physician assistants. Evaluations also indicate that secondary trainings may be more readily employed and accepted if administrative barriers are addressed early in the planning phases. © 2008 Brimmer et al; licensee BioMed Central Ltd.

Axe E.K., Satz P., Fawzy F.I.

Cognitive function and major depression in chronic fatigue: The apathy construct

2008 Journal of Chronic Fatigue Syndrome 14 (4); 19 – 38

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67650295810&partnerID=40>

Departments of Epidemiology, University of California, Los Angeles; Departments of Neuropsychology, University of California, Los Angeles; Departments of Psychiatry and Biobehavioral Science, University of California, Los Angeles; 915 Georgina Avenue, Santa Monica, CA 90402

Objective: The current study examined cognitive function, major depressive disorder (MDD), and apathy construct symptoms in a large multi-site surveillance study of chronic fatigue syndrome conducted by the Centers for Disease Control and Prevention. **Method:** Subjects underwent neuropsychological testing and were administered the Diagnostic Interview Schedule to establish psychiatric diagnoses. Questions in the Beck Depression Inventory relating to motivation were used to develop an apathy construct. **Results:** Neuropsychological test results showed impairment in multiple cognitive domains in over 25% of the cohort, and raised proportions of outliers in motor and executive function. Memory complaints were not associated with tests of memory function. The apathy construct rather than MDD was associated with impaired cognition. **Conclusions:** Impaired cognition in chronic fatigue does not appear to be associated with MDD but rather with endorsement

of construct symptoms. Similar associations were reported in medical conditions with known etiologies. These results suggest a potential biological basis for apathy construct symptoms. © 2008 by Informa Healthcare USA, Inc.

Andersen M.M., Permin H., Albrecht F.

Nine-year follow-up of Danish chronic fatigue syndrome (CFS) patients impact on health, social, vocational, and personal lives

2008 Journal of Chronic Fatigue Syndrome 14 (2); 7 – 23

<http://www.scopus.com/inward/record.url?eid=2-s2.0-39049130568&partnerID=40>

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Objective: To determine quality of life (QOL) and health in Danish CFS patients 9 years after diagnosis. Methods: Thirty-four adults with CFS responded to questions regarding QOL at diagnosis, and again 5 and 9 years later. At 9-year follow-up patients also responded to questions regarding health, fatigue, use of Health Care system, alcohol and exercise. Results: Two patients (6%) had recovered and 3 patients (10%) had received secondary diagnoses. Overall, there was no improvement, except with depression/anxiety. The order of severity among disabilities remained the same. Work had the highest disability score, followed by post-exertional malaise. Patients slept and rested 13.6 hours a day (mean). Self-reported physical health correlated with hours sleeping and resting. Rheumatic symptoms dominated the health symptoms. Alcohol consumption was low, and the use of the Health Care system was modest. Conclusion: After 9 years QOL was the same as at diagnosis, only mental health had improved. Copyright © by The Haworth Press, Inc. All rights reserved.

Amsterdam J.D., Shults J., Rutherford N.

Open-label study of s-citalopram therapy of chronic fatigue syndrome and co-morbid major depressive disorder

2008 Progress in Neuro-Psychopharmacology and Biological Psychiatry 32 (1); 100 – 106

<http://www.scopus.com/inward/record.url?eid=2-s2.0-38349074503&partnerID=40>

Depression Research Unit, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, United States; Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA, United States

Objective: Chronic fatigue syndrome (CFS) is a debilitating disorder with prominent symptoms of malaise, fatigue, myalgia, arthralgia, and impaired concentration. The symptoms of CFS may often overlap those of Major Depressive Disorder (MDD). Treatment of CFS has generally been disappointing. We hypothesized that s-citalopram therapy may improve the symptoms of both disorders in CFS patients with co-morbid depression. Methods: 16 patients received s-citalopram 10 mg to 20 mg daily for up to 12 weeks. Outcome measures of CFS included the Chalder Fatigue Questionnaire (CFQ), the multi-dimensional Fatigue Impact Scale (FIS), the CFS symptom rating (CFS-SR) 100 mm visual analogue scale, and the clinical global impressions severity (CGI/S) and change (CGI/C) ratings. Secondary outcomes of MDD included the Hamilton Depression Rating (HAM-D), Beck Depression Inventory (BDI), and the CGI/S and CGI/C ratings of MDD. Results: We observed reductions in the mean CFQ score ($p < 0.0005$), FIS score ($p < 0.0005$), and CGI/S ($p < 0.0005$) and CGI/C ($p < 0.0005$) ratings over time. There was a significant improvement in 5 of the 8 CFS-SR symptoms: post-exertion malaise ($p = 0.001$), headaches ($p < 0.0005$), un-refreshing sleep ($p < 0.0005$), and impaired memory and concentration ($p < 0.0005$). There was also a reduction in mean HAM-D ($p < 0.0005$), BDI ($p < 0.0005$), CGI/S ($p = 0.001$) and CGI/C ($p < 0.0005$) ratings of MDD. Limitations: The sample size was limited and the study design was not double-blind or placebo controlled. Conclusion: We observed a significant reduction in both CFS and co-morbid MDD symptom severity ratings, and improvement in 5 of 8 core somatic symptoms of CFS during s-citalopram therapy. © 2007 Elsevier Inc. All rights reserved.

Allen P.R.

Chronic Fatigue Syndrome: Implications for Women and their Health Care Providers During the Childbearing Years

2008 Journal of Midwifery and Women's Health 53 (4); 289 – 301

<http://www.scopus.com/inward/record.url?eid=2-s2.0-45849146905&partnerID=40>

Chronic fatigue syndrome is a complex debilitating medical disorder that affects approximately 4 million persons in the United States, predominantly women. There has been little scientific exploration about the experience of pregnancy, childbirth, and the postpartum period for women with this disorder. A review of the literature and current research findings addressing the epidemiology, diagnosis, symptoms, and treatment of chronic fatigue syndrome are presented, as well as the currently available data regarding the experience of women with chronic fatigue syndrome anticipating or experiencing pregnancy and the postpartum period. Expert opinion is presented along with current evidence to provide guidelines for the care of women with chronic fatigue syndrome during pregnancy, labor and birth, lactation, and the postpartum period. © 2008 American College of Nurse-Midwives.

Friedberg F., Sohl S.J.

Memory for fatigue in chronic fatigue syndrome: The relation between weekly recall and momentary ratings

2008 International Journal of Behavioral Medicine 15 (1); 29 – 33

<http://www.scopus.com/inward/record.url?eid=2-s2.0-41349088203&partnerID=40>

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Background: Understanding how patients with chronic fatigue syndrome (CFS) recall their fatigue is important because fatigue is a core clinical dimension of this poorly understood illness. Purpose: This study assessed the associations between momentary fatigue ratings and weekly recall of fatigue in 71 participants with CFS. Method: During the three-week data collection period, fatigue intensity was recorded six times a day in electronic diaries. At the end of each week, participants were asked to recall their fatigue intensity for that week. Statistical analyses were done with t-tests and Pearson's and intraclass correlations. Results: Average weekly recall of fatigue intensity was significantly higher than average momentary ratings. Furthermore, moderate to high Pearson's correlations and intraclass correlations (consistency and absolute agreement) between recall and momentary fatigue ratings were found. Conclusion: Individuals with CFS recalled consistently higher levels of fatigue in comparison to real-time momentary ratings, yet the level of agreement between the two measures was moderate to high. These findings may have implications for the conduct of office examinations for CFS. Copyright © Taylor & Francis Group, LLC.

Yao R.

The thoughts and methods for clinical research on acupuncture treatment of chronic fatigue syndrome

2007 Journal of Traditional Chinese Medicine 27 (3); 163 – 165

<http://www.scopus.com/inward/record.url?eid=2-s2.0-35348892694&partnerID=40>

The College of Traditional Chinese Medicine, Hong Kong University, Hong Kong, Hong Kong The general situation of chronic fatigue syndrome (CFS) and the criteria for its diagnosis are discussed, and it is put forward that making qi and blood of the zang-fu organs balanced is the key to acupuncture treatment of the disease. Such aspects as case selection, point selection and therapeutic assessment are also discussed in the present paper.

White P.D., Sharpe M.C., Chalder T., DeCesare J.C., Walwyn R.
Protocol for the PACE trial: A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/ myalgic encephalomyelitis or encephalopathy

2007 BMC Neurology 7

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34047242666&partnerID=40>

Department of Psychological Medicine, Queen Mary School of Medicine and Dentistry, St Bartholomew's Hospital, London, United Kingdom; Psychological Medicine and Symptoms Research Group, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, United Kingdom; Academic Department of Psychological Medicine, Guy's, King's and St Thomas' School of Medicine, Weston Education Centre, London, United Kingdom; PACE Trial Coordinating Centre, Queen Mary School of Medicine and Dentistry, St Bartholomew's Hospital, London, United Kingdom; Mental Health and Neuroscience Clinical Trials Unit (MH and N CTU), Institute of Psychiatry, London, United Kingdom

Background: Chronic fatigue syndrome (CFS, also called myalgic encephalomyelitis/encephalopathy or ME) is a debilitating condition with no known cause or cure. Improvement may occur with medical care and additional therapies of pacing, cognitive behavioural therapy and graded exercise therapy. The latter two therapies have been found to be efficacious in small trials, but patient organisations' surveys have reported adverse effects. Although pacing has been advocated by patient organisations, it lacks empirical support. Specialist medical care is commonly provided but its efficacy when given alone is not established. This trial compares the efficacy of the additional therapies when added to specialist medical care against specialist medical care alone. Methods/Design: 600 patients, who meet operationalised diagnostic criteria for CFS, will be recruited from secondary care into a randomised trial of four treatments, stratified by current comorbid depressive episode and different CFS/ME criteria. The four treatments are standardised specialist medical care either given alone, or with adaptive pacing therapy or cognitive behaviour therapy or graded exercise therapy. Supplementary therapies will involve fourteen sessions over 23 weeks and a 'booster session' at 36 weeks. Outcome will be assessed at 12, 24, and 52 weeks after randomisation. Two primary outcomes of self-rated fatigue and physical function will assess differential effects of each treatment on these measures. Secondary outcomes include adverse events and reactions, subjective measures of symptoms, mood, sleep and function and objective measures of physical activity, fitness, cost-effectiveness and cost-utility. The primary analysis will be based on intention to treat and will use logistic regression models to compare treatments. Secondary outcomes will be analysed by repeated measures analysis of variance with a linear mixed model. All analyses will allow for stratification factors. Mediators and moderators will be explored using multiple linear and logistic regression techniques with interactive terms, with the sample split into two to allow validation of the initial models. Economic analyses will incorporate sensitivity measures. Discussion: The results of the trial will provide information about the benefits and adverse effects of these treatments, their cost-effectiveness and cost-utility, the process of clinical improvement and the predictors of efficacy. © 2007 White et al; licensee BioMed Central Ltd.

Weatherburn G.C., Goldsmith Lister A., Findley L.J.

The feasibility of reviewing chronic fatigue syndrome clients at a distance: A teleconference pilot study

2007 Journal of Chronic Fatigue Syndrome 14 (1); 23 – 32

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34249322355&partnerID=40>

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Objective: There continues to be a shortage of clinical staff specialising in the treatment of CFS (ME). In order to access specialist care, many clients have to undertake long or difficult journeys

that may exacerbate their symptoms. This exploratory study aimed to reduce these travel problems by the introduction of a Teleconference Review Clinic (TRC). Method: A TRC was booked for six CFS clients who would normally have face-to-face review by specialists 44 miles away. Questionnaires were used to elicit the views of both clients being reviewed and clinicians undertaking the review at a distance. Differences in distances travelled by clients for conventional face to face and telemedicine review were calculated and comments about the teleconference made by clients and therapists were noted. Results: There was general satisfaction with the quality of the pictures and sound during the reviews. Clinicians were able to obtain all the information required to undertake all clinical assessments. For two clients the clinical management was changed after the consultation and for one client an issue was identified that required referral to another clinician. For clients who lived nearer to the teleconference hospital, the journey saved ranged between 1 mile and 85.8 miles, the mean being 64.2 miles. Conclusion: This pilot study does suggest that telemedicine in this area of medicine is logistically viable and effective, and indicates that a larger study is needed. Copyright © by The Haworth Press, Inc. All rights reserved.

Thanawala S., Taylor R.R.

Service utilization, barriers to service access, and coping in adults with chronic fatigue syndrome

2007 Journal of Chronic Fatigue Syndrome 14 (1); 5 – 21

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34249335699&partnerID=40>

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Objective: In a sample of 47 adults with CFS, we aimed to describe patterns of service utilization, identify barriers to service access, and explore the relationship between service utilization and coping styles. Method: A questionnaire assessing service utilization frequency and barriers to service access was administered to a sample of 47 individuals with CFS. The Illness Management Questionnaire was used to assess relationships between coping styles and service utilization. Results: A Cochran's Q test of homogeneity revealed that medical and CFS self-help services were most frequently used and rehabilitation services were least frequently used. In terms of service accessibility, 80.9% of participants reported at least one barrier. Lack of financial (including insurance) resources and lack of knowledge about service availability were the two most frequently reported. In terms of coping styles, symptom focusing was positively associated with use of CFS self-help services and with use of in-home services and social service agencies. Information seeking was negatively associated with use of in-home and social service agencies and with use of mental health services. Conclusion: These findings can be used by health-care professionals and advocacy-based organizations to develop programs focused on mass education campaigns for health-care providers, increase knowledge of service availability among individuals with CFS, and to understand relationships between certain types of coping styles and service preferences. Copyright © by The Haworth Press, Inc. All rights reserved.

Scheeres K., Wensing M., Mes C., Bleijenberg G.

The impact of informational interventions about cognitive behavioral therapy for chronic fatigue syndrome on GPs referral behavior

2007 Patient Education and Counseling 68 (1); 29 – 32

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34547197358&partnerID=40>

Expert Centre Chronic Fatigue, Radboud University Nijmegen Medical Centre, Netherlands; Centre for Quality of Care Research, Radboud University Nijmegen Medical Centre, Netherlands; Roessingh Research and Development Enschede, Netherlands

Objective: This study investigated the impact of an informational intervention among general practitioners (GPs) about a new treatment with cognitive behavioral therapy (CBT) for chronic fatigue syndrome (CFS) in a mental health center (MHC). The outcome measures concerned GPs

knowledge and attitudes towards CFS and their actual referrals of CFS patients to this new treatment setting. Methods: Three hundred and one GPs, who all had received written information about CFS four times, and who partly had also visited an informational group session, completed a short questionnaire survey on CFS knowledge and attitudes. Referral data were obtained from the mental health center. Results: During 16 months 22% of all GPs in the concerning region had referred at least one CFS patient. Concerning knowledge and attitude, the survey results showed that 70% of the GPs had remembered the intervention's main message, namely the new treatment possibility. These informed GPs reported better knowledge and more positive attitudes towards CFS than the non-informed GPs, who had not seen and read the intervention's information. Conclusion: This study showed that disseminating written materials can be a useful method for stimulating GPs to refer CFS patients for CBT. Practice implications: In future implementation projects concerning CBT for CFS (or other 'new' treatments for a disputed illness) in a MHC or other institution, the informational intervention evaluated here can be a suitable and efficient method to inform GPs and let them refer patients. © 2007 Elsevier Ireland Ltd. All rights reserved.

Quarmby L., Rimes K.A., Deale A., Wessely S., Chalder T.
Cognitive-behaviour therapy for chronic fatigue syndrome: Comparison of outcomes within and outside the confines of a randomised controlled trial

2007 Behaviour Research and Therapy 45 (6); 1085 – 1094

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34247101869&partnerID=40>

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Outcomes for cognitive-behaviour therapy (CBT) in randomised controlled trials (RCTs) have rarely been compared to those in routine clinical practice. Taking the case of CBT for chronic fatigue syndrome (CFS), we evaluated the results of a successful RCT against those of the same treatment given in the same setting as part of routine practice. Fatigue and social adjustment scores were compared for patients who received CBT for CFS as part of a RCT (N = 30) and patients who received CBT as part of everyday clinical practice (N = 384). The results in the RCT were superior to those in routine clinical practice. Between pre-treatment and 6-month follow-up, the RCT showed a larger reduction in fatigue and greater improvement in social adjustment than those in routine treatment. The changes in fatigue scores were similar for both groups during treatment but were greater in the RCT between post-treatment and follow-up. Potential reasons for the superior results of the RCT include patient selection, therapist factors and the use of a manualised treatment protocol. Practitioners need to pay particular attention to relapse prevention and ensuring adequate follow-up in addition to encouraging patients to continue with cognitive-behavioural strategies once treatment has ended. © 2006 Elsevier Ltd. All rights reserved.

Kuo D.Z., Cheng T.L., Rowe P.C.
Successful use of a primary care practice-specialty collaboration in the care of an adolescent with chronic fatigue syndrome

2007 Pediatrics 120 (6)

<http://www.scopus.com/inward/record.url?eid=2-s2.0-36849057075&partnerID=40>

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We report on the successful collaborative care of an adolescent with chronic fatigue syndrome between a primary care pediatrician and an academic chronic fatigue syndrome specialist located in

different cities. Regular telephone and e-mail communication and clearly defined patient-care roles allowed for timely management of symptoms and marked clinical improvement. We discuss ways to improve the collaboration of primary care and subspecialty physicians for patients with chronic fatigue syndrome and children with special health care needs. Copyright © 2007 by the American Academy of Pediatrics.

Knoop H., Prins J.B., Stulemeijer M., Van Der Meer J.W.M., Bleijenberg G.
The effect of cognitive behaviour therapy for chronic fatigue syndrome on self-reported cognitive impairments and neuropsychological test performance

2007 Journal of Neurology, Neurosurgery and Psychiatry 78 (4); 434 – 436

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33947732897&partnerID=40>

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Background: Patients with chronic fatigue syndrome (CFS) often have concentration and memory problems. Neuropsychological test performance is impaired in at least a subgroup of patients with CFS. Cognitive behavioural therapy (CBT) for CFS leads to a reduction in fatigue and disabilities. Aim: To test the hypothesis that CBT results in a reduction of self-reported cognitive impairment and in an improved neuropsychological test performance. Methods: Data of two previous randomised controlled trials were used. One study compared CBT for adult patients with CFS, with two control conditions. The second study compared CBT for adolescent patients with a waiting list condition. Self-reported cognitive impairment was assessed with questionnaires. Information speed was measured with simple and choice reaction time tasks. Adults also completed the symbol digit-modalities task, a measure of complex attentional function. Results: In both studies, the level of self-reported cognitive impairment decreased significantly more after CBT than in the control conditions. Neuropsychological test performance did not improve. Conclusions: CBT leads to a reduction in self-reported cognitive impairment, but not to improved neuropsychological test performance. The findings of this study support the idea that the distorted perception of cognitive processes is more central to CFS than actual cognitive performance.

Knoop H., Bleijenberg G., Gielissen M.F.M., Van Der Meer J.W.M., White P.D.
Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome?

2007 Psychotherapy and Psychosomatics 76 (3); 171 – 176

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34147194092&partnerID=40>

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Background: Cognitive behavioural therapy (CBT) for chronic fatigue syndrome (CFS) leads to a decrease in symptoms and disabilities. There is controversy about the nature of the change following treatment; some suggest that patients improve by learning to adapt to a chronic condition, others think that recovery is possible. The objective of this study was to find out whether recovery from CFS is possible after CBT. Methods: The outcome of a cohort of 96 patients treated for CFS with CBT was studied. The definition of recovery was based on the absence of the criteria for CFS set up by the Center for Disease Control (CDC), but also took into account the perception of the patients'

fatigue and their own health. Data from healthy population norms were used in calculating conservative thresholds for recovery. Results: After treatment, 69% of the patients no longer met the CDC criteria for CFS. The percentage of recovered patients depended on the criteria used for recovery. Using the most comprehensive definition of recovery, 23% of the patients fully recovered. Fewer patients with a co-morbid medical condition recovered. Conclusion: Significant improvement following CBT is probable and a full recovery is possible. Sharing this information with patients can raise the expectations of the treatment, which may enhance outcomes without raising false hopes. Copyright © 2007 S. Karger AG.

Jones J.F., Maloney E.M., Boneva R.S., Jones A.-B., Reeves W.C.
Complementary and alternative medical therapy utilization by people with chronic fatiguing illnesses in the United States

2007 BMC Complementary and Alternative Medicine 7

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34249893347&partnerID=40>

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Background: Chronic fatiguing illnesses, including chronic fatigue syndrome (CFS), pose a diagnostic and therapeutic challenge. Previous clinical reports addressed the utilization of health care provided to patients with CFS by a variety of practitioners with other than allopathic training, but did not examine the spectrum of complementary and alternative medicine (CAM) therapies used. This study was designed to measure CAM therapy use by persons with fatiguing illnesses in the United States population. Methods: During a random-digit dialing survey to estimate the prevalence of CFS-like illness in urban and rural populations from different geographic regions of the United States, we queried the utilization of CAM including manipulation or body-based therapies, alternative medical systems, mind-body, biologically-based, and energy modalities. Results: Four hundred forty fatigued and 444 non-fatigued persons from 2,728 households completed screening. Fatigued subjects included 53 persons with prolonged fatigue, 338 with chronic fatigue, and 49 with CFS-like illness. Mind-body therapy (primarily personal prayer and prayer by others) was the most frequently used CAM across all groups. Among women, there was a significant trend of increasing overall CAM use across all subgroups (p -trend = 0.003). All categories of CAM use were associated with significantly poorer physical health scores, and all but one (alternative medicine systems) were associated with significantly poorer mental health scores. People with CFS-like illness were significantly more likely to use body-based therapy (chiropractic and massage) than non-fatigued participants (OR = 2.52, CI = 1.32, 4.82). Use of body-based therapies increased significantly in a linear trend across subgroups of non-fatigued, prolonged fatigued, chronic fatigued, and CFS-like subjects (p -trend = 0.002). People with chronic fatigue were also significantly more likely to use body-based therapy (OR = 1.52, CI = 1.07, 2.16) and mind-body (excluding prayer) therapy than non-fatigued participants (OR = 1.73, CI = 1.20 - 2.48). Conclusion: Utilization of CAM as common in fatiguing illnesses, and was largely accounted for by the presence of underlying conditions and poor physical and mental health. Compared to non-fatigued persons, those with CFS-like illness or chronic fatigue were most likely to use body-based and mind-body therapies. These observations have important implications for provider education programs and development of intervention strategies for CFS. © 2007 Jones et al; licensee BioMed Central Ltd.

Jason L.A., Torres-Harding S., Friedberg F., Corradi K., Njoku M.G., Donalek J., Reynolds N., Brown M., Weitner B.B., Rademaker A., Papernik M.

Non-pharmacologic interventions for CFS: A randomized trial

2007 Journal of Clinical Psychology in Medical Settings 14 (4); 275 - 296

<http://www.scopus.com/inward/record.url?eid=2-s2.0-37448998708&partnerID=40>

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Non-pharmacological behavioral treatments for CFS have been suggested as promising. These trials have tested protocols composed of behavioral, cognitive and cognitive-behavioral interventions but there have been few efforts to differentially evaluate their outcomes. The primary purpose of the current study was to evaluate the effectiveness of nurse delivered non-pharmacologic interventions. In the present study, 114 participants diagnosed with CFS were randomly assigned to four 6-month interventions. The interventions were: cognitive-behavior therapy, cognitive therapy, anaerobic activity, and a relaxation control group. The study found that these interventions led to increases in several areas of functioning, with more consistent changes occurring among those participants in the cognitive condition. For the 25 variables in this study, significant change occurred for 28%, 20%, 16%, and 12% of the variables for the cognitive, cognitive behavior therapy, anaerobic activity, and relaxation conditions, respectively. However, the majority of participants continued to be diagnosed with CFS following the treatment trial. Implications of these findings are discussed. © Springer Science+Business Media, LLC 2007.

Jason L.A., Corradi K., Torres-Harding S.R.

Toward an empirical case definition of CFS

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-38049186625&partnerID=40>

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The current case definition of chronic fatigue syndrome (CFS) was developed by consensus rather than empirical methods. From a practice point of view, if the case definition is not empirically-based, it is possible that some individuals with this illness might not be diagnosed, and others who do not have the disorder might be diagnosed. In the present study, 114 individuals with CFS were provided a theoretically driven questionnaire that featured neuropsychiatric, vascular, inflammatory, muscle/joint, infectious, and other symptoms. When symptoms using this classification were factor analyzed, a more interpretable factor structure was identified than when using symptoms from traditional case definition criteria. Factor scores from the new classification system were cluster analyzed, and four types of patient groups were identified. The field of CFS studies needs to be grounded in empirical methods for determining a case definition versus more consensus-based efforts. Such efforts will ultimately help social service providers better diagnose and provide services to those with this chronic illness. © Copyright (c) by The Haworth Press, Inc. All rights reserved.

Guo J.

Chronic fatigue syndrome treated by acupuncture and moxibustion in combination with psychological approaches in 310 cases

2007 Journal of Traditional Chinese Medicine 27 (2); 92 – 95

<http://www.scopus.com/inward/record.url?eid=2-s2.0-36148981805&partnerID=40>

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Objective: To observe clinical therapeutic effect of acupuncture and moxibustion combined with a psychological approach on chronic fatigue syndrome (CFS). Methods: The treatment was given by acupuncture plus moxibustion combined with a psychological approach based on differentiation of symptoms and signs in 310 cases. Results: Of 310 cases observed, 275 cases (88.7%) were clinically cured, 28 cases (9%) improved, and 7 cases (2.3%) failed. Conclusion: Acupuncture plus moxibustion combined with a psychological approach is an effective therapy for CFS.

Godfrey E., Chalder T., Ridsdale L., Seed P., Ogden J.

Investigating the 'active ingredients' of cognitive behaviour therapy and counselling for patients with chronic fatigue in primary care: Developing a new process measure to assess treatment fidelity and predict outcome

2007 British Journal of Clinical Psychology 46 (3); 253 – 272

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34548274533&partnerID=40>

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Objectives. To develop a brief measure of the therapy process and use it to examine which therapeutic ingredients were associated with outcome in a sample of patients from a randomized controlled trial (RCT) of cognitive behaviour therapy (CBT) versus counselling for patients with chronic fatigue in primary care. It was hypothesized that the two therapies would be clearly distinguishable and that in terms of process variables, the therapeutic alliance would be important in predicting outcome. Design. The data for this study were collected alongside a RCT in primary care and included audiotaped therapy sessions. These tapes were assessed by two independent raters using a newly devised measure in order to evaluate therapy process and its relationship with outcome. Methods. Tapes from 71 patients participating in the RCT were assessed to form the basis of the process analysis. Outcome was self-reported fatigue symptoms at 6 months follow-up. Data reduction was achieved via a principal component analysis (PCA). Factors were entered into a multiple regression analysis to produce a final model of predictors of outcome. Results. The process measure showed that although the treatments could be distinguished, there was some overlap between them. The key predictor of a good fatigue outcome was emotional processing, including the expression, acknowledgement and acceptance of emotional distress. Conclusion. A new process measure was developed successfully which now warrants further testing. It was able to assess treatment adherence and unpack, and distinguish the common factor which predicted outcome across therapy modalities. The findings lend preliminary support to the view that the specific techniques associated with particular 'brand names' of therapy are not necessarily the 'active ingredients' that help patient's change within the primary care setting. Emotional processing predicted outcome for patients with chronic fatigue and therefore future research might explore this in more depth, in order to understand better how it can be facilitated. © 2007 The British Psychological Society.

Burley L., Cox D.L., Findley L.J.
Severe Chronic Fatigue Syndrome (CFS/ME): Recovery is possible

2007 British Journal of Occupational Therapy 70 (8); 339 - 344

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34548400878&partnerID=40>

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The recovery of individuals with very severe chronic fatigue syndrome/ myalgic encephalomyelitis (CFS/ME) is possible with successful multidisciplinary management. This case vignette aims to highlight the beneficial outcome of using occupational therapy lifestyle management and the Canadian Occupational Performance Measure to identify perceived problems in occupational performance and indicate change. The current management strategies in CFS/ME are discussed briefly and the challenges of the management of severe CFS/ME are described, indicating a need for a supportive team and specialist inpatient services. In 2003, the Department of Health released funds in England to develop more widely accessible CFS/ME services. This case study illustrates a positive outcome for one individual with severe CFS/ME, following admission to a specialist inpatient facility. It is hoped that it may aid other therapists working with and developing services for people with severe presentations of CFS/ME.

Brown M.M., Jason L.A.

Functioning in individuals with chronic fatigue syndrome: Increased impairment with co-occurring multiple chemical sensitivity and fibromyalgia

2007 Dynamic Medicine 6

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34250199030&partnerID=40>

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Background. Chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), and fibromyalgia (FM) commonly co-occur. Some propose that CFS, MCS, and FM are manifestations of the same illness based on high rates of co-occurrence and overlapping diagnostic criteria. This study seeks to differentiate these diagnoses by comparing individuals with one or more illness on functioning, psychiatric comorbidity, coping style, and in vivo physical measures. Methods. Participants included 114 men and women who met criteria for CFS. FM was diagnosed during a physical examination, and MCS was assessed using a questionnaire. Participants were divided into four groups: CFS alone, CFS-MCS, CFS-FM, and CFS-MCS-FM. Self-report measures, a psychiatric interview, and in vivo physical measures were given. Results. 43.9% met criteria for CFS alone, 23.7% met criteria for CFS-MCS, 15.8% met criteria for CFS-FM, and 16.7% met criteria for CFS-MCS-FM. The CFS-MCS-FM group was more disabled than the CFS alone group on measures of physical functioning, general health, and bodily pain. In vivo measures did not differ, but the CFS-MCS-FM group rated exertion higher than the CFS alone group. Conclusion. Individuals with CFS alone were the highest functioning group across several domains, such as disability, depression, and severity of symptoms. Participants with three diagnoses experienced the greatest amount of disability. While substantial co-occurrence of these illnesses was found, this study provides evidence that having more than one illness exacerbates one's disability beyond CFS alone. © 2007 Brown and Jason; licensee BioMed Central Ltd.

Parvu L., Nichita C., Giurginca M., Meghea A.

Selective plant extracts with application in the therapy of chronic fatigue syndrome

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-35548998709&partnerID=40>

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Chronic fatigue syndrome (CFS) is a very complex disorder with uncertain cause characterized by a chronic fatigue that persists at least six months. Among possible causes of this illness, epidemiological studies indicate primarily viral or bacterial infection and secondary some chronic diseases such as: allergies, autoimmune diseases, etc. Referring to biochemical mechanism of this disorder, studies performed in clinical and non-clinical experiment show a high oxidative stress at the level of blood, brain and liver tissues. Since clinical studies revealed encouraging results at the treatment of the affected subjects with plant extracts, this work aims at obtaining and testing scavenger properties of three selective plant extracts, as a major condition for the obtaining a new natural drug with application in the therapy of CFS.

Wearden A.J., Riste L., Dowrick C., Chew-Graham C., Bentall R.P., Morriss R.K., Peters S., Dunn G., Richardson G., Lovell K., Powell P.

Fatigue Intervention by Nurses Evaluation - The FINE Trial. A randomised controlled trial of nurse led self-help treatment for patients in primary care with chronic fatigue syndrome: Study protocol. [ISRCTN74156610]

2006 BMC Medicine 4

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646265026&partnerID=40>

School of Psychological Sciences, University of Manchester, Manchester M13 9PL, United Kingdom; School of Population Community and Behavioural Sciences, University of Liverpool, Liverpool L69 3GB, United Kingdom; Division of Primary Care, Rusholme Academic Unit, University of Manchester, Manchester M14 5NP, United Kingdom; Department of Psychiatry, Queens Medical Centre, University of Nottingham, Nottingham NG7 2UH, United Kingdom; Division of Psychiatry, University of Liverpool, Liverpool L69 3GA, United Kingdom; Division of Epidemiology and Health Sciences, University of Manchester, Manchester M13 9PT, United Kingdom; Centre for Health Economics, University of York, York YO10 5DD, United Kingdom; School of Nursing Midwifery and Social Work, University of Manchester, Manchester M13 9PL, United Kingdom; Infectious Diseases Unit, Royal Liverpool University Hospital, Liverpool L7 8XP, United Kingdom

Background: Chronic fatigue syndrome, also known as ME (CFS/ME), is a condition characterised primarily by severe, disabling fatigue, of unknown origin, which has a poor prognosis and serious personal and economic consequences. Evidence for the effectiveness of any treatment for CFS/ME in primary care, where most patients are seen, is sparse. Recently, a brief, pragmatic treatment for CFS/ME, based on a physiological dysregulation model of the condition, was shown to be successful in improving fatigue and physical functioning in patients in secondary care. The treatment involves providing patients with a readily understandable explanation of their symptoms, from which flows the rationale for a graded rehabilitative plan, developed collaboratively with the therapist. The present trial will test the effectiveness and cost-effectiveness of pragmatic rehabilitation when delivered by specially trained general nurses in primary care. We selected a client-centred counselling intervention, called supportive listening, as a comparison treatment. Counselling has been shown to be as effective as cognitive behaviour therapy for treating fatigue in primary care, is more readily available, and controls for supportive therapist contact time. Our control condition is treatment as usual by the general practitioner (GP). Methods and design: This study protocol describes the design of an ongoing, single-blind, pragmatic randomized controlled trial of a brief (18 week) self-help treatment, pragmatic rehabilitation, delivered by specially trained nurse-therapists in patients' homes, compared with nurse-therapist delivered supportive listening and treatment as usual by the GP. An economic evaluation, taking a societal viewpoint, is being carried out alongside

the clinical trial. Three adult general nurses were trained over a six month period to deliver the two interventions. Patients aged over 18 and fulfilling the Oxford criteria for CFS are assessed at baseline, after the intervention, and again one year later. Primary outcomes are self-reported physical functioning and fatigue at one year, and will be analysed on an intention-to-treat basis. A qualitative study will examine the interventions' mechanisms of change, and also GPs' drivers and barriers towards referral. © 2006 Wearden et al; licensee BioMed Central Ltd.

Vermeulen R.C.W.

Translation and validation of the Dutch language version of the CDC Symptom Inventory for assessment of Chronic Fatigue Syndrome (CFS)

2006 Population Health Metrics 4

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33750405026&partnerID=40>

CFS and Pain Research Center Amsterdam, Amsterdam, Netherlands

Background: In a study by Wagner et al., the CDC Symptom Inventory was validated in a population selected from the inhabitants of a city in the USA, and proofed reliable for the assessment of the accompanying symptoms of CFS. The Dutch translation of the CDC Symptom Inventory is compared to the original and the psychometric properties are presented for patients in a tertiary care setting. Methods: One hundred thirty-nine consecutive patients who visited the CFS Center Amsterdam for the first time were asked to complete the CDC Symptom Inventory in the Dutch Language Version (DLV) together with the usual set of questionnaires. Sixty-one patients had Chronic Fatigue (CF) and 78 patients fulfilled the criteria for CFS. Forty-three healthy accompanying persons completed the CDC Symptom Inventory DLV, the Physical Functioning scale of the Medical Outcome Survey Short Form-36 DLV, and the Fatigue and Concentration scales of the Checklist Individual Strength (CIS-20). Results: The healthy controls group contained fewer women and was overall older than the patient groups. The influence of gender on the CDC Symptom Inventory DLV was significant but the effect of age was not. The Dutch version had a good internal consistency and convergent validity. The results were comparable to the original English version, but the sex-related difference needs further study. Conclusion: The Dutch version of the CDC Symptom Inventory is a reliable tool for the assessment of the secondary criteria for CFS. The results show that it is comparable to the outcome of studies in English speaking countries. © 2006 Vermeulen; licensee BioMed Central Ltd.

Van Houdenhove B., Bruyninckx K., Luyten P.

In search of a new balance. Can high "action-proneness" in patients with chronic fatigue syndrome be changed by a multidisciplinary group treatment?

2006 Journal of Psychosomatic Research 60 (6); 623 – 625

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646797742&partnerID=40>

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Objective: The purpose of this study is to investigate changes in action-proneness (a cognitive and behavioral tendency toward direct action) after a multidisciplinary group intervention, including cognitive behaviour therapy (CBT) and graded exercise therapy (GET). Methods: Patients with chronic fatigue syndrome (n=62) completed three versions of a Dutch self-report questionnaire evaluating action-proneness retrospectively that is (1) before illness onset, (2) before treatment and (3) after treatment. Significant others (n=62) also gave their opinion about the patients' action-proneness at time points 1 and 2. Results: Premorbid action-proneness levels considerably dropped after illness onset. After treatment, action-proneness levels significantly increased again, although levels remained below premorbid levels. Conclusion: High action-proneness retrospectively reported by CFS patients can be adaptively modified by a multidisciplinary group treatment including CBT and GET. © 2006 Elsevier Inc. All rights reserved.

Van De Putte E.M., Engelbert R.H.H., Kuis W., Kimpfen J.L.L., Uiterwaal C.S.P.M.
How fatigue is related to other somatic symptoms

2006 Archives of Disease in Childhood 91 (10); 824 – 827

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33749465105&partnerID=40>

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Aims: To assess the relation between fatigue and somatic symptoms in healthy adolescents and adolescents with chronic fatigue syndrome/myalgic encephalopathy (CFS/ME). **Methods:** Seventy two adolescents with CFS were compared within a cross-sectional study design with 167 healthy controls. Fatigue and somatic complaints were measured using self-report questionnaires, respectively the subscale subjective fatigue of the Checklist Individual Strength (CIS-20) and the Children's Somatization Inventory. **Results:** Healthy adolescents reported the same somatic symptoms as adolescents with CFS/ME, but with a lower score of severity. The top 10 somatic complaints were the same: low energy, headache, heaviness in arms/legs, dizziness, sore muscles, hot/cold spells, weakness in body parts, pain in joints, nausea/upset stomach, back pain. There was a clear positive relation between log somatic symptoms and fatigue (linear regression coefficient: 0.041 points log somatic complaints per score point fatigue, 95% CI 0.033 to 0.049) which did not depend on disease status. **Conclusions:** Results suggest a continuum with a gradual transition from fatigue with associated symptoms in healthy adolescents to the symptom complex of CFS/ME.

Toda K., Kimura H.

Efficacy of neurotropin in chronic fatigue syndrome: A case report

2006 Hiroshima Journal of Medical Sciences 55 (1); 35 – 37

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646021585&partnerID=40>

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Chronic fatigue syndrome (CFS) is a disorder that causes general fatigue and chronic wide-spread pain. A 28-year-old male visited an outpatient department due to general fatigue and pain involving the entire body. He did not suffer from fibromyalgia, but he was diagnosed with CFS. At the initial visit, he complained of lack of concentration, memory decline, frequent urination, insomnia and occasional difficulty of emotional control, as well as general fatigue and pain involving the entire body. Four tablets of Neurotropin per day alone were administered. General fatigue and pain were gradually alleviated one week later. His sleep condition, concentration power, and memory also improved two weeks later. Medication was discontinued from 11 weeks based on the patient's judgment as he felt little general fatigue and pain involving the entire body. Treatment was completed 3 months later. The symptoms disappeared and did not recur five months after the discontinuation of Neurotropin. He was looking for a job without fatigue and pain 8 months later (5 months after the cessation of treatment). The functional mechanisms of Neurotropin in CFS are unknown.

Thomas M.A., Smith A.P.

An investigation of the long-term benefits of antidepressant medication in the recovery of patients with chronic fatigue syndrome

2006 Human Psychopharmacology 21 (8); 503 – 509

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33846084724&partnerID=40>

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Two hundred and seventy-five patients fulfilling the Centre for Disease Control (CDC) criteria for Chronic Fatigue Syndrome (CFS) completed measures assessing illness history, global ratings of well being, sleep, activity and psychopathology at baseline, 6 months, 18 months and 3 year follow-up. Forty-nine of these patients had been prescribed antidepressant medication, namely Tricyclic drugs or Selective Serotonin Re-uptake Inhibitors (SSRI). Data from the current study suggests that patients in the antidepressant medication group recover at a faster rate over time when compared to the untreated patient sample. In addition, the positive effects of antidepressant therapy are maintained at the 3-year follow-up point. It appears from these data that the SSRI in particular are responsible for improvements in the condition. Most importantly, these improvements include a reduction in the levels of fatigue recorded by patients. These findings have not been demonstrated in previous studies of the effect of antidepressant therapy for patients with this illness and this may reflect the short time periods studied in the earlier research. Copyright © 2006 John Wiley & Sons, Ltd.

Tharakan B., Dhanasekaran M., Brown-Borg H.M., Manyam B.V.

Trichopus zeylanicus combats fatigue without amphetamine-mimetic activity

2006 Phytotherapy Research 20 (3); 165 - 168

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33645471475&partnerID=40>

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Chronic fatigue is a complex and little understood symptom for which there is no safe and effective pharmacotherapy. The present study was conducted to investigate the effectiveness of *Trichopus zeylanicus* whole plant powder on fatigue in young Sprague Dawley rats, and aged normal and long-living mutant Ames dwarf mice. Fatigue was evaluated by subjecting the animals to a forced swim test. *Trichopus zeylanicus* (250 and 500 mg/kg) treated young Sprague-Dawley rats resisted fatigue at a significant level ($p < 0.005$) compared with controls by an extended swim time in the forced swim test. Oral *Trichopus zeylanicus* (500 mg/kg) treatment for 2 weeks significantly increased the mobility time in the aged mutant ($p < 0.05$) and normal mice ($p < 0.01$) and significantly increased the swim time in the forced swim test in the aged normal mice ($p < 0.05$). Amphetamine-mimetic activity in *Trichopus zeylanicus* was excluded by suitable tests. These results show that *Trichopus zeylanicus* whole plant powder has anti-fatigue effects in young Sprague-Dawley rats and aged normal and mutant Ames dwarf mice providing scientific evidence for the Kani tribal practice in India. Copyright © 2006 John Wiley & Sons, Ltd.

Taylor R.R., Thanawala S.G., Shiraishi Y., Schoeny M.E.

Long-term outcomes of an integrative rehabilitation program on quality of life: A follow-up study

2006 Journal of Psychosomatic Research 61 (6); 835 – 839

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33751436379&partnerID=40>

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Objective: To assess the long-term effects of an integrative rehabilitation program on the overall quality of life of individuals with chronic fatigue syndrome (CFS). Methods: This study utilized a within-subjects, repeated measures cohort design. Twenty-three subjects diagnosed with CFS attended eight sessions of an illness-management group followed by 7 months of goal-oriented, individualized counseling that occurred once weekly for 30 min per session. Quality of life was assessed at five time points (baseline, following the group phase, following the one-on-one phase, and 4 and 12 months following program completion). Results: A within-subjects repeated measures ANOVA revealed significant increases in overall quality of life for up to 1 year following program completion [$F(4, 21)=23.5, P<.001$]. Conclusions: Definitive conclusions about program efficacy are limited by design issues. However, findings suggest that the program may have led to improvement in quality of life for up to 1 year following program completion. © 2006 Elsevier Inc. All rights reserved.

Taylor R.R., Jason L.A., Shiraishi Y., Schoeny M.E., Keller J.

Conservation of resources theory, perceived stress, and chronic fatigue syndrome: Outcomes of a consumer-driven rehabilitation program

2006 Rehabilitation Psychology 51 (2); 157 - 165

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33745071760&partnerID=40>

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Objective: To evaluate the impact of a consumer-driven rehabilitation program on perceptions of loss and gain of interpersonal relationships, energy, material objects, work benefits and opportunities, well-being, and experiences of mastery in persons with chronic fatigue syndrome. Study Design: Participants were randomly assigned to a program group ($n = 23$) or a control group ($n = 24$). Outcomes were assessed (a) at baseline, (b) after program participants completed an illness management group, and (c) after they completed one-on-one peer counseling. Setting: A community-based advocacy organization for individuals with disabilities. Interventions: Four months of illness management groups followed by 7 months of one-on-one peer counseling emphasizing goal setting and goal attainment. Main Outcome Measure: The Conservation of Resources Evaluation scale. Results: Significant gains were observed for program participants across all categories of resource gain - interpersonal, energy, material, work, well-being, and mastery resources. Effect sizes were moderate to large. Conclusions: Programs in which participatory action research methods are used may have a positive impact on resource acquisition for individuals with chronic fatigue syndrome. Copyright 2006 by the American Psychological Association.

Shor S.
Lyme disease presenting as chronic fatigue syndrome

2006 Journal of Chronic Fatigue Syndrome 13 (4); 67 – 75

<http://www.scopus.com/inward/record.url?eid=2-s2.0-35948972822&partnerID=40>

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Objective: Chronic Fatigue Syndrome (CFS) by definition represents a diagnosis of exclusion. Late stage or "Chronic Lyme" infection with or without "co-infections" is a difficult diagnosis to establish. The symptom complex of both conditions can be very similar. This case study represents an attempt to support serious consideration for a subpopulation of patients otherwise diagnosed with "CFS," as actually representing chronic Lyme disease. Method: A case study is presented of a 33-year-old man, who for two years, was being managed as having CFS. However, after $\hat{\wedge}$ 1/2 years of utilizing multiple modalities of management with limited success, the diagnosis of Lyme was reconsidered. Historical exposure risks to Lyme in this individual were high. He had prolonged exposure in the highly tick-infested mountains of North Carolina for 18 months, several years prior to becoming ill. More aggressive investigation confirmed the diagnosis of Lyme. Appropriate changes in management were associated with an improved level of functioning that was far in excess of what maximal management of CFS was able to achieve. The features of CFS and chronic Lyme can be very similar and include the following: Profound fatigue often associated with cognitive impairment. Other common symptoms related to both of these conditions include sleep disturbances, fibromyalgia, and dysautonomias. In pursuing clarification of this diagnosis, the author was exposed to a contrast in medical opinion regarding diagnostic tools and criteria that were perceived as creating potential barriers to the management of patients presenting with these symptoms. Conclusion: Acceptance and awareness of the possibility that Lyme disease can present as CFS has important therapeutic and prognostic implications. © Copyright by The Haworth Press, Inc. All rights reserved.

Schonfeldt-Lecuona C., Connemann B.J., Wolf R.C., Braun M., Freudenmann R.W.
Bupropion augmentation in the treatment of chronic fatigue syndrome with coexistent major depression episode: A case report

2006 Pharmacopsychiatry 39 (4); 152 - 154

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33746871099&partnerID=40>

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While psychoeducational strategies and general support are always indicated for the treatment of chronic fatigue syndrome (CFS), pharmacological strategies are yet not well established. Antidepressants such as selective serotonin re-uptake inhibitors have been shown to influence positively symptoms and immunological parameters. However, a considerable part of CFS patients do not satisfactorily respond to them. Bupropion, a centrally acting catecholamine-transporter blocker without classic psycho-analeptic properties, shows theoretical potential to improve fatigue symptoms. In the reported case paroxetine was augmented with bupropion at high dosage, a strategy which consecutively led to a rapid relief of CFS-symptoms. © Georg Thieme Verlag KG Stuttgart.

Sankey A., Hill C.M., Brown J., Quinn L., Fletcher A.

A follow-up study of chronic fatigue syndrome in children and adolescents: Symptom persistence and school absenteeism

2006 *Clinical Child Psychology and Psychiatry* 11 (1); 126 – 138

<http://www.scopus.com/inward/record.url?eid=2-s2.0-31944444182&partnerID=40>

Southampton City Primary Care Trust, United Kingdom; Southampton University, United Kingdom; Southampton General Hospital, United Kingdom; St Andrews Hospital, Northampton, United Kingdom; Princess Royal Hospital, Haywards Heath, United Kingdom; Ashurst Child and Family Mental Health Services, Ashurst Hospital, Lyndhurst Rd, Ashurst, Southampton, SO40 7AR, United Kingdom; Community Child Health; Bursledon House, Southampton General Hospital, United Kingdom This is a follow-up study of 28 young people aged between 7 and 17 meeting the Oxford criteria for the diagnosis of chronic fatigue syndrome treated in a specialist paediatric/psychiatric service. Retrospective case note analysis revealed a wide range and duration of symptoms together with high levels of school absenteeism prior to the diagnosis. The mean follow-up interval after discharge from the specialist service was 3 years and although most of the young people regarded themselves as fully recovered by this time, improvement was variable and about one third were still experiencing disabling symptoms. The illness had impacted on the education or career plans of all the young people to some extent with 15 experiencing difficulty returning to school. This article highlights the need for early recognition and diagnosis of chronic fatigue syndrome in young people and the importance of continuing paediatric support to reduce symptom persistence in the sensitive recovery period. Maintaining school attendance by close liaison between health and education services both before and after diagnosis and treatment is also vital if long-term morbidity is to be reduced. Copyright © 2006 SAGE Publications.

Saidi G., Haines L.

The management of children with chronic fatigue syndrome-like illness in primary care: A cross-sectional study

2006 *British Journal of General Practice* 56 (522); 43 – 47

<http://www.scopus.com/inward/record.url?eid=2-s2.0-30444435931&partnerID=40>

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Background: Most studies on children with chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) have been undertaken in tertiary care and little is known about their management in primary care. Aim: To describe the characteristics of patients aged 5-19 years with CFS-like illness in primary care and to examine how GPs investigate and manage patients. Design of study: Descriptive retrospective questionnaire study. Setting: Sixty-two UK GP practices in the MRC General Practice Research Framework (GPRF). Method: One hundred and twenty-two practices were approached; 62 identified 116 patients consulting a GP with severe fatigue lasting over 3 months. Practice nurses and GPs completed questionnaires from medical notes and patients completed postal questionnaires. Results: Ninety-four patients were considered by a clinical panel, blind to diagnosis, to meet the Oxford CFS criteria with a fatigue duration of 3 months. Seventy-three per cent were girls, 94% white, mean age was 12.9 years and median illness duration 3.3 years. GPs had principal responsibility for 62%. A diagnosis of CFS/ME was made in 55%, 30% of these within 6 months. Fifty per cent had a moderate illness severity. Paediatric referrals were made in 82% and psychiatric referrals in 46% (median time of 2 and 13 months respectively). Advice given included setting activity goals, pacing, rest and graded exercise. Conclusions: Patient characteristics are comparable to those reported in tertiary care, although fewer are severe cases. GPs have responsibility for the majority of patients, are diagnosing CFS/ME within a short time and applying a range of referral and advice strategies. ©British Journal of General Practice 2006.

Saggini R., Vecchiet J., Iezzi S., Racciatti D., Affaitati G., Bellomo R.G., Pizzigallo E.
Submaximal aerobic exercise with mechanical vibrations improves the functional status of patients with chronic fatigue syndrome

2006 Europa Medicophysica 42 (2); 97 - 102

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33745914947&partnerID=40>

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Aim. Chronic fatigue syndrome (CFS) is an illness characterised by disabling fatigue of uncertain aetiology and other nonspecific symptoms. Typically CFS patients complain of a severe fatigue made worse by exercise, with a consistent reduction of working activity. A physical deconditioning could explain CFS features as well as a neuromuscular dysfunction, of central or peripheric origin. **Methods.** Ten CFS patients were enrolled in a protocol of a rehabilitative treatment over a six-month period: they underwent a submaximal and predominantly aerobic exercise with a reduced O₂ consumption using a Galileo 2000 system that provides mechanical vibrations characterised by sinusoid vertical solicitations. Before and after such treatment, all patients underwent a pressure pain thresholds profile, an evaluation of physical and psychosocial parameters using the visual analogue scale (VAS) of Scott-Huskisson, and a muscle performance analysis by the CIBEX 6000 dynamometer. **Results.** After the six-month period of study there was an overall improvement of the above described parameters as compared to the basal determinations. **Conclusion.** We conclude that the rehabilitative exertion provides an useful treatment for CFS patients particularly to realize an effective training of the explosive strength.

Reynolds F., Vivat B.

Narratives of art-making in chronic fatigue syndrome/myalgic encephalomyelitis: Three case studies

2006 Arts in Psychotherapy 33 (5); 435 - 445

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33750623044&partnerID=40>

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This paper explores the narratives of three women who had lived with severe chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) for many years, and who engaged in art-making as a leisure activity rather than for psychotherapy. Three distinct narratives about the role of art-making in CFS/ME were inferred. One participant represented art as a way of filling time rather than having further psychological significance. In her narrative, art provided satisfaction but also functioned as a witness to time and opportunity that had been lost to an unchanging illness. The second participant narrated both illness and art-making as intertwined journeys towards a more able and useful self. Her narrative had features of the quest described in previous typologies. The third participant also provided a quest narrative, but her struggle focused inwards on understanding her feelings about her illness and its effects on her life. The analytic focus on narrative revealed the distinctive constructions of illness and art-making that are usually submerged when qualitative analysis focuses on themes common to groups of participants. These narratives of art-making in CFS/ME have relevance to understanding the multi-faceted therapeutic benefits of art. © 2006 Elsevier Inc. All rights reserved.

Pardaens K., Haagdoorens L., Van Wambeke P., Van den Broeck A., Van Houdenhove B.
How relevant are exercise capacity measures for evaluating treatment effects in chronic fatigue syndrome? results from a prospective, multidisciplinary outcome study

2006 Clinical Rehabilitation 20 (1); 56 - 66

<http://www.scopus.com/inward/record.url?eid=2-s2.0-32644463155&partnerID=40>

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Objective: To evaluate the outcome of a multidisciplinary treatment programme for patients with chronic fatigue syndrome, including health-related quality of life (HRQoL) and psychosocial variables, and exercise capacity measures. Design: A six-month prospective outcome study. Setting: University outpatient rehabilitation clinic; group setting. Subjects: One hundred and sixteen women fulfilling chronic fatigue syndrome criteria. Interventions: Cognitive behaviourally and graded exercise-based strategies; emphasis on adaptive lifestyle changes. Measures: Short Form General Health Survey (SF-36); Symptom Checklist (SCL-90); Causal Attribution List (CAL); Self-Efficacy Scale (SE); maximum progressive bicycle ergometer test with respiratory gas analysis; and isokinetic leg strength test, before and after treatment. Results: The total group significantly improved on nearly all reported HRQoL/psychosocial variables. Changes in exercise capacity measures were rather modest and did not correlate or only weakly correlated with HRQoL/psychosocial variables. Subgroup analyses indicated that less fit patients improved significantly more on exercise capacity measures than their more fit counterparts. Patients who were fitter at baseline scored better on pretreatment HRQoL/psychosocial variables, but both subgroups improved similarly on these variables. Conclusions: Health-related quality of life and psychosocial functioning in patients with chronic fatigue syndrome improves after a six-month cognitive behaviourally and graded exercise-based multidisciplinary treatment programme. Increase in exercise capacity measures is not a necessary condition for reported improvements, except for less fit patients. © 2006 Edward Arnold (Publishers) Ltd.

O'Dowd H., Gladwell P., Rogers C.A., Hollinghurst S., Gregory A.
Cognitive behavioural therapy in chronic fatigue syndrome: A randomised controlled trial of an outpatient group programme

2006 Health Technology Assessment 10; 37

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33751230219&partnerID=40>

Pain Management Centre, Frenchay Hospital, Bristol, United Kingdom; Bristol Heart Institute, Bristol Royal Infirmary, Bristol, United Kingdom; Department of Community Based Medicine, University of Bristol, Bristol, United Kingdom

Objectives: To test the hypothesis that group cognitive behavioural therapy (CBT) will produce an effective and cost-effective management strategy for patients in primary care with chronic fatigue syndrome/ myalgic encephalopathy (CFS/ME). Design: A double-blind, randomised controlled trial was adopted with three arms. Outcomes were assessed at baseline and 6 and 12 months after first assessment and results were analysed on an intention-to-treat basis. Setting: A health psychology department for the management of chronic illness in a general hospital in Bristol, UK. Participants: Adults with a diagnosis of CFS/ME referred by their GP. Interventions: The three interventions were group CBT incorporating graded activity scheduling, education and support group (EAS) and standard medical care (SMC). Outcome measures: The primary outcome measure was the Short Form with 36 Items (SF-36) physical and mental health summary scales. Other outcome measures included the Chalder fatigue scale, Hospital Anxiety and Depression Scale, General Health Questionnaire, physical function (shuttles walked, walking speed and perceived fatigue), health utilities index and cognitive function (mood, recall and reaction times). Results: A total of 153 patients were recruited to the trial and 52 were randomised to receive CBT, 50 to EAS and 51 to SMC. Twelve patients failed to attend for the 12-month follow-up and 19 patients attended one follow-up, but not both. The sample was found to be representative of the patient group and the characteristics of the three groups were similar at baseline. Three outcome measures, SF-36 mental

health score, Chalder fatigue scale and walking speed, showed statistically significant differences between the groups. Patients in the CBT group had significantly higher mental health scores [difference +4.35, 95% confidence interval (CI) +0.72 to +7.97, $p = 0.019$], less fatigue (difference -2.61, 95% CI -4.92 to -0.30, $p = 0.027$) and were able to walk faster (difference +2.83 shuttles, 95% CI +1.12 to +5.53, $p = 0.0013$) than patients in the SMC group. CBT patients also walked faster and were less fatigued than those randomised to EAS (walking speed: difference +1.77, 95% CI +0.025 to +3.51, $p = 0.047$; fatigue: difference -3.16, 95% CI -5.59 to -0.74, $p = 0.011$). Overall, no other statistically significant difference across the groups was found, although for many measures a trend towards an improved outcome with CBT was seen. Except for walking speed, which, on average, increased by +0.87 shuttles (95% CI +0.09 to +1.65, $p = 0.029$) between the 6- and 12-month follow-ups, the scores were similar at 6 and 12 months. At baseline, 30% of patients had an SF-36 physical score within the normal range and 52% had an SF-36 mental health score in the normal range. At 12 months, the physical score was in the normal range for 46% of the CBT group, 26% of the EAS group and 44% of SMC patients. For mental health score the percentages were CBT 74%, EAS 67% and SMC 70%. Of the CBT group, 32% showed at least a 15% increase in physical function and 64% achieved a similar improvement in their mental health. For the EAS and SMC groups, this improvement in physical and mental health was achieved for 40 and 60% (EAS) and 49 and 53% (SMC), respectively. The cost-effectiveness of the intervention proved very difficult to assess and did not yield reliable conclusions. Conclusions: Group CBT did not achieve the expected change in the primary outcome measure as a significant number did not achieve scores within the normal range post-intervention. The treatment did not return a significant number of subjects to within the normal range on this domain; however, significant improvements were evident in some areas. Group CBT was effective in treating symptoms of fatigue, mood and physical fitness in CFS/ME. It was found to be as effective as trials using individual therapy in these domains. However, it did not bring about improvement in cognitive function or quality of life. There was also evidence of improvement in the EAS group, which indicates that there is limited value in the non-specific effects of therapy. Further research is needed to develop better outcome measures, assessments of the broader costs of the illness and a clearer picture of the characteristics best fitted to this type of intervention. © Queen's Printer and Controller of HMSO 2006. All rights reserved.

McCue P., Buchanan T., Martin C.R.

Screening for psychological distress using internet administration of the Hospital Anxiety and Depression Scale (HADS) in individuals with chronic fatigue syndrome

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Objectives. To investigate the factor structure and internal consistency of the Hospital Anxiety and Depression Scale (HADS) in individuals with Chronic Fatigue Syndrome (CFS) using an Internet administered version of the instrument. Design. Between subjects. Method. Confirmatory factor analysis (CFA) and internal consistency analysis of the HADS was used to determine the psychometric characteristics of the instrument in individuals with CFS and a control group with data captured via an Internet data collection protocol. Results. CFA revealed that a 3-factor solution offered the most parsimonious account of the data. Internal consistency estimations of the anxiety and depression subscales were found to be acceptable for both groups. The CFS group was found to have significantly higher HADS-assessed anxiety and depression scores compared with controls, however, there was also evidence found that Internet administration of the instrument may inflate HADS subscale scores as an artifact of testing medium. Conclusions. The HADS is suitable for use for screening individuals with CFS in terms of the factor structure of the instrument, however, clinicians should be aware that this instrument assesses 3 domains of affective disturbance rather than 2 as is interpreted within the current HADS anxiety and depression subscale scoring system. Researchers need also be aware that Internet administration of negative affective state measures such as the

HADS is likely to inflate scores and need to ensure that comparisons between clinical groups are made with control group data gathered using the same collection methodology. © 2006 The British Psychological Society.

Li Y., Liu H., Feng S., Gong D.

The therapeutic effects of electrical acupuncture and auricular-plaster in 32 cases of chronic fatigue syndrome

2006 Journal of Traditional Chinese Medicine 26 (3); 163 – 164

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33749635459&partnerID=40>

Guangzhou University of Traditional Chinese Medicine, Guangzhou 510405, China; Tongji Hospital, Foshan, Guangdong 528000, China; Acupuncture and Massage College, Guangzhou University of Traditional Chinese Medicine, Guangzhou 510405, China

Objective: To observe the therapeutic effects of electrical acupuncture and auricular-plaster therapy for chronic fatigue syndrome (CFS). Method: 64 CFS patients were randomly divided into two groups. 32 cases in the treatment group were treated by the electrical acupuncture and auricular-plaster therapy, and 32 cases in the control group with oral hydrocortisone. Results: The total effective rates were respectively 93.75% in the treatment group and 75.00% in the control group, with a statistically significant difference between the two groups ($P < 0.05$). Conclusion: Electrical acupuncture and auricular-plaster therapy may show a better anti-fatigue effect than that of routine Western drugs.

Leydon G.M., Raine R.

The need to act versus reluctance to act: A qualitative study of primary care antidepressant prescribing for patients with common somatic conditions of uncertain cause

2006 Primary Care Mental Health 4 (2); 131 – 142

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34249993486&partnerID=40>

Primary Medical Care, Community Clinical Sciences Division, University of Southampton Medical School, Southampton, United Kingdom; Department of Epidemiology and Public Health, UCL, London, United Kingdom; Community Clinical Sciences Division, University of Southampton Medical School, Aldermoor Health Centre, Aldermoor Close, Southampton SO16 5ST, United Kingdom

Background: The National Institute for Clinical Excellence recently called on doctors to exercise more caution in prescribing antidepressants. Antidepressants are used in the management of patients with common somatic conditions of uncertain cause. The factors influencing the prescribing of antidepressants to this group of patients are not fully understood. Aim: To explore general practitioners' and mental health professionals' perspectives on the use of antidepressants for patients with chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS) and chronic back pain (CBP). Design of study: A randomly selected sample of general practitioners and mental health practitioners in England were invited to participate in one of 16 focus group discussions. Clinical scenarios, including the use of antidepressants for patients with CFS, IBS and CBP, were discussed. Setting: Meeting room, outside participants' work environment. Methods: Purposive sample of six groups. Each comprised 9-13 participants (49 GPs and 15 mental health practitioners). Group talk was thematically analysed to identify their views on antidepressant prescribing. Results: Two overarching and opposing themes emerged. The first was the need to act. Reasons for action included: lack of clear research evidence, desire to help patients, and a need for GPs to maintain their own self-worth. The second theme was a reluctance to act/prescribe antidepressants because of the potential for harm, their short-term effects and preference for somatic treatments for IBS and CBP. Conclusions: The perception that action is preferable to inaction poses a barrier to effective clinical practice and can lead to internal conflict between practitioners' beliefs and actions. © 2006 Radcliffe Publishing.

Jason L.A., Bell D.S., Rowe K., Van Hoof E.L.S., Jordan K., Lapp C., Gurwitt A., Miike T., Torres-Harding S., De Meirleir K.

A pediatric case definition for myalgic encephalomyelitis and chronic fatigue syndrome

2006 Journal of Chronic Fatigue Syndrome 13 (02-Mar); 1 – 44

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33847364381&partnerID=40>

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For a diagnosis of chronic fatigue syndrome (CFS), most researchers use criteria that were developed by Fukuda et al. (1994), with modifications suggested by Reeves et al. (2003). However, this case definition was established for adults rather than children. A Canadian Case Definition (ME/CFS; Myalgic Encephalomyelitis/CFS) has recently been developed, with more specific inclusion criteria (Carruthers et al., 2003). Again, the primary aim of this case definition is to diagnose adult CFS. A significant problem in the literature is the lack of both a pediatric definition of ME/CFS and a reliable instrument to assess it. These deficiencies can lead to criterion variance problems resulting in studies labeling children with a wide variety of symptoms as having ME/CFS. Subsequently, comparisons between articles become more difficult, decreasing the possibility of conducting a meta-analysis. This article presents recommendations developed by the International Association of Chronic Fatigue Syndrome Pediatric Case Definition Working group for a ME/CFS pediatric case definition. It is hoped that this pediatric case definition will lead to more appropriate identification of children and adolescents with ME/CFS. © 2006 by The Haworth Press, Inc. All rights reserved.

Hyland M.E., Sodergren S.C., Lewith G.T.

Chronic fatigue syndrome: The role of positivity to illness in chronic fatigue syndrome patients

2006 Journal of Health Psychology 11 (5); 731 – 741

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33746889012&partnerID=40>

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Fifty-three chronic fatigue syndrome patients treated at a complementary medical centre were assessed over 12 months. Measures included the Chalder Fatigue scale, the General Health Questionnaire (GHQ) and positivity in illness (Silver Lining Questionnaire, SLO). The SLO measured at 6 and 9 months predicted ($p < .01$) mental (but not physical) fatigue at 12 months independently of current mental fatigue, initial mental fatigue, duration since diagnosis and time between start of treatment and entry to the study. The GHQ did not predict fatigue at any time point. The results suggest that a caring therapeutic intervention increases positive interpretations of illness prior to improvements in mental fatigue, but that positivity does not play a causal role in the reduction of fatigue. Copyright © 2006 SAGE Publications.

Hjermstad M.J., Oldervoll L., Fossa S.D., Holte H., Jacobsen A.B., Loge J.H.
Quality of life in long-term Hodgkin's disease survivors with chronic fatigue

2006 European Journal of Cancer 42 (3); 327 – 333

<http://www.scopus.com/inward/record.url?eid=2-s2.0-31144463573&partnerID=40>

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The prevalence of chronic fatigue (CF), elevated fatigue levels >six months, is 2.5-3 times higher in long-term Hodgkin disease survivors (HDSs) than in the general population (GP). This is the first study comparing the quality of life (QoL) of chronic fatigued survivors with that of chronic fatigued subjects in the GP. The fatigue questionnaire (FQ) and the SF-36 were mailed to 591 HDSs successfully treated at the Norwegian Radium Hospital from 1971 to 1997. Patient data were compared with nationally representative GP data, adjusted for age, gender and education. The response rate was 80% (N = 475), median follow-up 195 months (range 53-431), mean age 46 years (range 21-74), and 44% were females. HDSs reported significantly poorer QoL than the GP with lower scores on six of eight SF-36 scales (P < 0.001). The subgroup of HDSs with chronic fatigue however (N = 142/475, 30%) had better QoL on five of eight SF-36 scales than subjects with CF in the GP (N = 224/2141, 11%), particularly mental health and emotional role-functioning (P = 0.005 and <0.0001). No differences were found on the physical SF-36 domains. Overall, HDSs reported lower QoL than the GP, in particular the HDSs with CF. Their QoL was similar to that of GP subjects with CF, but with significantly better mental health status. This suggests that CF in long-term survivors may be associated with more physical than psychological aspects of long-term cancer survivorship. © 2005 Elsevier Ltd. All rights reserved.

Hawkins C., Jason L.A., Torres-Harding S.R.
Reliability of a chronic fatigue syndrome questionnaire

2006 Journal of Chronic Fatigue Syndrome 13 (4); 41 – 66

<http://www.scopus.com/inward/record.url?eid=2-s2.0-35948978494&partnerID=40>

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Background: A diagnostic instrument, the CFS Questionnaire, was developed for clinicians and researchers to administer to their patients as a screening instrument for CFS. The CFS Questionnaire is comprehensive, covering the inclusionary and exclusionary self-report criteria of the current U.S. case definition (Fukuda et al. 1999). The instrument also assesses past and current activity levels, and symptoms of post-exertional malaise to ensure these items are adequately assessed. Objectives: The goal of the present study was to evaluate the diagnostic reliability of an experimental measure for assessing chronic fatigue syndrome (CFS). Methods: This instrument was administered to 15 persons with CFS, 15 persons with major depressive disorder (MDD), and 15 controls. Using the Fukuda et al. (1994) diagnostic criteria, raters independently reviewed participants' CFS Questionnaire responses and rated whether each study participant met criteria for chronic fatigue syndrome. Results: This instrument demonstrated good inter-rater reliability. Further, this instrument demonstrated adequate classification accuracy, with a 9.3 positive likelihood ratio and a.08 negative likelihood ratio. Overall, the CFS Questionnaire demonstrated good test-retest reliability, with intra-class correlation coefficients and kappa coefficients at .70 or higher for most items. Lower test-retest reliability coefficients were found for some items assessing temporal symptoms or items requiring an estimate of time. Conclusion: The present study suggests that the CFS Questionnaire is a reliable diagnostic tool. Use of the CFS Questionnaire should

promote higher levels of diagnostic reliability because it allows for accurate classification of individuals with CFS. © Copyright by The Haworth Press, Inc. All rights reserved.

Gottfries C.-G., Hager O., Regland B., Zachrisson O.
Long-term treatment with a Staphylococcus toxoid vaccine in patients with fibromyalgia and chronic fatigue syndrome

2006 Journal of Chronic Fatigue Syndrome 13 (4); 29 – 40

<http://www.scopus.com/inward/record.url?eid=2-s2.0-35948954363&partnerID=40>

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One hundred and sixty patients with fibromyalgia and chronic fatigue syndrome, who were on a continuous treatment with a Staphylococcus vaccine, were followed during one year with repeated consultation visits. The patients had participated in controlled studies and been on continuous treatment with the vaccine for 22 \pm 10 months before inclusion into this follow-up study. They were treated with 1 mL of the vaccine subcutaneously every third to fourth week. Adverse events were few. The adherence to the treatment was very good. Over a period of one year, 8% withdrew, and in only 5%, the withdrawal was due to insufficient clinical effect. Only in two cases where the patients were allergic to the preservative of the vaccine, the side effects caused the withdrawal of the treatment. Ratings with scales (CPRS-15 and FibroFatigue) showed improvement from start of treatment and also further improvement during the follow-up year. In view of the natural history for these disorders the result is of interest. © Copyright by The Haworth Press, Inc. All rights reserved.

Garcia-Campayo J., Pascual A., Alda M., Marzo J., Magallon R., Fortes S.
The Spanish version of the FibroFatigue Scale: Validation of a questionnaire for the observer's assessment of fibromyalgia and chronic fatigue syndrome

2006 General Hospital Psychiatry 28 (2); 154 – 160

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33644638192&partnerID=40>

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Objective: To examine some of the psychometric properties of the Spanish version of the FibroFatigue Scale (FFS). Methods: FFS was administered to 120 patients diagnosed with fibromyalgia and chronic fatigue syndrome. Internal consistency was evaluated by using Cronbach's $\bar{I}\pm$, test-retest reliability with weighted kappa and construct validity by correlations among FFS, the Fibromyalgia Impact Questionnaire (FIQ), the EuroQol 5D (EQ-5D) and the Hospital Anxiety and Depression Scale (HADS). The interrater reliability was tested using analysis of variance with patients and raters as independent factors. Results: Internal consistency ($\bar{I}\pm$) was .88, test-retest reliability was .91, and interrater reliability was .93. Significant correlations were obtained between overall FFS and the FIQ (.55, $P<.01$), the EQ-5D (-.48, $P<.01$) and the HADS depression subscale (.25, $P<.01$), but not with the HADS anxiety subscale. Conclusion: These results support the reliability and validity of the data obtained with the Spanish version of the FFS. © 2006 Elsevier Inc. All rights reserved.

Demitrack M.A.

Clinical methodology and its implications for the study of therapeutic interventions for chronic fatigue syndrome: A commentary

2006 Pharmacogenomics 7 (3); 521 - 528

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646020699&partnerID=40>

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Chronic fatigue syndrome (CFS) is a complex, multisymptom illness of unknown etiology. A variety of operational case definitions based on symptom report have been developed that share some common clinical features. Patients often come to clinical presentation after months or, more typically, years of symptomatic distress. Comorbid presentation with psychiatric illnesses has been noted. Due to these fundamental issues, the impact of patient selection and the specification of the methods of outcome assessment loom large in therapeutic studies of CFS. While a substantial body of research has focused on increasing our understanding of the basic pathobiology of CFS, there have been comparatively fewer studies that have addressed the problems of patient characterization and outcome assessment. The role of clinical methodology in the study of the therapeutics of CFS is not trivial, and may confound our understanding of pragmatic recommendations for treatment. © 2006 Future Medicine Ltd.

Blockmans D., Persoons P., Van Houdenhove B., Bobbaers H.

Does methylphenidate reduce the symptoms of chronic fatigue syndrome?

2006 American Journal of Medicine 119; 2

<http://www.scopus.com/inward/record.url?eid=2-s2.0-31444449330&partnerID=40>

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PURPOSE: Chronic fatigue syndrome is a clinical entity consisting of prolonged and debilitating fatigue in which concentration disturbances are very frequent. Until now, no medical treatment has shown any efficacy. The objectives of this study were to investigate the short-term effects of methylphenidate, an amphetamine derivative, on fatigue, concentration disturbances, and quality of life. **SUBJECTS AND METHODS:** A double-blind randomized placebo-controlled crossover study was conducted in 60 patients who fulfilled the 1994 Centers for Disease Control criteria for chronic fatigue syndrome and had concentration difficulties. Patients were enrolled between March 2003 and March 2004 at the outpatient department of a university hospital referral center for chronic fatigue syndrome patients. Random assignment to 4 weeks treatment with methylphenidate 2 x 10 mg/day, followed by 4 weeks of placebo treatment, or 4 weeks of placebo treatment, followed by methylphenidate treatment. Fatigue and concentration were measured with a Checklist Individual Strength (CIS) and a Visual Analogue Scale (VAS). **RESULTS:** Fatigue scores fell significantly during methylphenidate intake in comparison with baseline (mean difference: -0.7, P = .010 for VAS; mean difference: -11.8, P <.0001 for CIS) and in comparison with placebo (mean difference: -1.0, P = .001 for VAS; mean difference: -9.7, P <.0001 for CIS). Concentration disturbances, measured with a VAS improved significantly under methylphenidate treatment compared with baseline (mean difference: -1.3, P <.0001) and compared with placebo (mean difference: -1.1, P <.0001). A clinical significant effect (≥33% improvement or CIS ≥76) on fatigue was achieved in 17% of patients, who were considered responders; on concentration in 22% of patients. **CONCLUSIONS:** Methylphenidate at a dose of 2 x 10 mg/day is significantly better than placebo in relieving fatigue and concentration disturbances in a minority of chronic fatigue syndrome patients. Further studies are needed to investigate the long-term effects of this treatment. © 2006 Elsevier Inc. All rights reserved.

Bazelmans E., Prins J., Bleijenberg G.
Cognitive Behavior Therapy for Relatively Active and for Passive Chronic Fatigue Syndrome Patients

2006 Cognitive and Behavioral Practice 13 (2); 157 – 166

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33646024022&partnerID=40>

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In chronic fatigue syndrome (CFS), facilitating, initiating, and perpetuating factors are distinguished. Although somatic factors might have initiated symptoms in CFS, they do not explain the persistence of fatigue. Cognitive behavior therapy (CBT) for CFS focuses on factors that perpetuate and prolong symptoms. Recently it has been shown that, based on their level of activity, two groups of patients can be distinguished. For so-called "relatively active" CFS patients, the main perpetuating factors are nonaccepting and demanding cognitions leading to bursts of activity. For so-called "passive" CFS patients, their fear that activity might worsen their symptoms (which results in an avoidance of activity) is the most important perpetuating factor. These differences in perpetuating factors result in separate treatment manuals for relatively active and for passive CFS patients. Before describing the treatment manuals, we outline basic assumptions, considerations before starting CBT for CFS, and ways to determine the activity pattern. © 2006 Association for Behavioral and Cognitive Therapies.

Ashby B., Wright B., Jordan J.

Chronic fatigue syndrome: An evaluation of a community based management programme for adolescents and their families

2006 Child and Adolescent Mental Health 11 (1); 13 – 18

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33644869625&partnerID=40>

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Background: Young people with chronic fatigue syndrome (CFS), families and clinicians may differ in their attributions about CFS and consequently in their approach to treatment. Research that clarifies the best treatment approaches is clearly needed. We have sought to develop a model that engages young people and their families in a collaborative way. The approach adopts an optimistic and holistic stance using an active rehabilitation model paying attention to the integrated nature of the physiological and psychological aspects of the illness. Method: This small study set out to evaluate this approach from a service user perspective. Semistructured interviews were carried out with young people and their parents separately in order to elicit their views on key treatment elements and their perceived degree of recovery. Results: Improvements are indicated in all key areas addressed and qualitative information suggests that families value this approach. Conclusion: Further research is needed to address treatment issues for families who choose not to opt into the service model. © 2005 Association for Child and Adolescent Mental Health.

Al-Haggar M.S., Al-Naggar Z.A., Abdel-Salam M.A.
Biofeedback and cognitive behavioral therapy for Egyptian adolescents suffering from chronic fatigue syndrome

2006 Journal of Pediatric Neurology 4 (3); 161 – 169

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33845526455&partnerID=40>

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We aimed to evaluate the efficacy of cognitive behavioral therapy (CBT) aided by biofeedback in rehabilitating Egyptian adolescents who were suffering from chronic fatigue syndrome (CFS). Out of 298 screened individuals with chronic fatigue, only 159 adolescents were eligible for study; of them 63 cases lost follow up and four cases were further excluded because of switch leaving only 92 cases with complete database. Age range of enrolled cases was 10-14 years and male/female ratio (1/2.5). They were recruited from private schools and polyclinics in Eastern province, Saudi Arabia; some cases were referred by psychiatrists in private hospitals of the same area. All cases were diagnosed as CFS according to the recommendations of International CFS Study Group. Patients were randomly allocated to one of two groups; interventional group comprised 50 cases and underwent CBT aided with biofeedback over a period of 18 months applying two protocols according to patient's activity pattern. Forty-two cases were followed and treated symptomatically and used as control group. Data were processed and analyzed using SPSS version 10.0. The most common symptoms were unrefreshing sleep, headache and myalgia (95.8%, 67.7% and 50% respectively). Patients of interventional group showed marked improvement manifested by decrement of checklist individual strength (decreased 23.1%; 95% confidence interval 19.2-25.4%) and better school attendance (increased 31.5%; 95% confidence interval 29.8-36.6 hours/ month) with the disappearance of some self-rated CFS symptoms. CBT aided by biofeedback could be very effective in treatment of adolescents suffering from CFS taking in consideration the stressors and precipitating factors during settings of psychotherapy. © 2006 IOS Press. All rights reserved.

Wright B., Ashby B., Beverley D., Calvert E., Jordan J., Miles J., Russell I., Williams C.
A feasibility study comparing two treatment approaches for chronic fatigue syndrome in adolescents

2005 Archives of Disease in Childhood 90 (4); 369 – 372

<http://www.scopus.com/inward/record.url?eid=2-s2.0-16844362931&partnerID=40>

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[No abstract available]

Winwood P.C., Winefield A.H., Dawson D., Lushington K.
Development and validation of a scale to measure work-related fatigue and recovery: The Occupational Fatigue Exhaustion/Recovery scale (OFER)

2005 Journal of Occupational and Environmental Medicine 47 (6); 594 – 606

<http://www.scopus.com/inward/record.url?eid=2-s2.0-20544450294&partnerID=40>

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Objective: Various empirical studies link persistent failure to recover from acute fatigue to the evolution of chronic fatigue. However, existing fatigue measurement scales do not tend to distinguish between acute and chronic fatigue elements well, and none include a measure of

effective recovery from fatigue. Methods: The 15 item Occupational Fatigue Exhaustion Recovery (OFER) scale has been developed and validated in three study populations specifically to measure work-related fatigue. Results: The OFER scale possesses robust, gender-bias free psychometric characteristics. Its three subscales identify and distinguish between chronic work-related fatigue traits, acute end-of-shift states and effective fatigue recovery between shifts. Conclusion: These studies confirm the mediating role of intershift-shift recovery in the evolution of adaptive end-of-shift fatigue states to maladaptive persistent fatigue traits. The OFER scale is suggested as a potentially valuable new tool for use in work-related fatigue research. Copyright © by American College of Occupational and Environmental Medicine.

Wagner D., Nisenbaum R., Heim C., Jones J.F., Unger E.R., Reeves W.C.
Psychometric properties of the CDC Symptom Inventory for assessment of Chronic Fatigue Syndrome

2005 Population Health Metrics 3

<http://www.scopus.com/inward/record.url?eid=2-s2.0-27344459789&partnerID=40>

Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, 1600 Clifton Rd., Atlanta, GA, United States; St Michaels Hospital, Inner City Health Research Unit, Toronto, Ont., Canada; Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, United States

Objectives: Validated or standardized self-report questionnaires used in research studies and clinical evaluation of chronic fatigue syndrome (CFS) generally focus on the assessment of fatigue. There are relatively few published questionnaires that evaluate case defining and other accompanying symptoms in CFS. This paper introduces the self-report CDC CFS Symptom Inventory and analyzes its psychometric properties. Methods: One hundred sixty-four subjects (with CFS, other fatiguing illnesses and non fatigued controls) identified from the general population of Wichita, Kansas were enrolled. Evaluation included a physical examination, a standardized psychiatric interview, three previously validated self-report questionnaires measuring fatigue and illness impact (Medical Outcomes Survey Short-Form-36 [MOS SF-36], Multidimensional Fatigue Inventory [MFI], Chalder Fatigue Scale), and the CDC CFS Symptom Inventory. Based on theoretical assumptions and statistical analyses, we developed several different Symptom Inventory scores and evaluated them on their ability to differentiate between participants with CFS and non-fatigued controls. Results: The Symptom Inventory had good internal consistency and excellent convergent validity. A Total score (all symptoms), Case Definition score (CFS case defining symptoms) and Short Form score (6 symptoms with minimal correlation) differentiated CFS cases from controls. Furthermore, both the Case Definition and Short Form scores distinguished people with CFS from fatigued subjects who did not meet criteria for CFS. Conclusion: The Symptom Inventory appears to be a reliable and valid instrument to assess symptoms that accompany CFS. It is a positive addition to existing instruments measuring fatigue because it allows other dimensions of the illness to be assessed. Further research is needed to confirm and replicate the current findings in a normative population. © 2005 Wagner et al; licensee BioMed Central Ltd.

Surawy C., Roberts J., Silver A.

The effect of mindfulness training on mood and measures of fatigue, activity, and quality of life in patients with chronic fatigue syndrome on a hospital waiting list: A series of exploratory studies

2005 Behavioural and Cognitive Psychotherapy 33 (1); 103 – 109

<http://www.scopus.com/inward/record.url?eid=2-s2.0-12944270429&partnerID=40>

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Three exploratory studies evaluated group mindfulness training (which aims to facilitate non-judgmental attention to present moment experience through the practice of meditation) in patients

waiting for cognitive behaviour therapy for Chronic Fatigue Syndrome (CFS). The approaches used were based on Mindfulness Based Stress Reduction, and Mindfulness Based Cognitive Therapy. The first group showed that such training is acceptable to patients and that it results in significantly improved subjective measures of anxiety, and improvements in subjective levels of fatigue that approached significance, when compared to waiting list controls. A second uncontrolled study replicated the findings of the first study and also demonstrated an improvement in quality of life as measured by the Fatigue Impact Scale (FIS). More wide-ranging effects were demonstrated in the final study in which significant improvements in subjective levels of fatigue, anxiety, depression, quality of life and physical functioning were observed following the training programme. These effects were sustained for 3 months. Overall, the findings of the three exploratory studies indicate that MBSR/MBCT has potential for the treatment of patients with CFS.

Sullivan P.F., Pedersen N.L., Jacks A., Evengard B.
Chronic fatigue in a population sample: Definitions and heterogeneity

2005 Psychological Medicine 35 (9); 1337 – 1348

<http://www.scopus.com/inward/record.url?eid=2-s2.0-24644497677&partnerID=40>

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Background. Numerous nosological decisions are made when moving from the common human symptom of unusual fatigue to the rare chronic fatigue syndrome (CFS). These decisions have infrequently been subjected to rigorous evaluation. Method. We obtained telephone interview data on fatiguing symptoms from 31 406 individuals twins in the Swedish Twin Registry aged 42-64 years; 5330 subjects who endorsed fatigue and possessed no exclusionary condition formed the analytic group. We evaluated the definition and classification of CFS-like illness using graphical methods, regression models, and latent class analysis. Results. Our results raise fundamental questions about the 1994 Centers for Disease Control criteria as (1) there was no empirical support for the requirement of four of eight cardinal CFS symptoms; (2) these eight symptoms were not equivalent in their capacity to predict fatigue; and (3) no combination of symptoms was markedly more heritable. Critically, latent class analysis identified a syndrome strongly resembling CFS-like illness. Conclusions. Our data are consistent with the 'existence' of CFS-like illness although the dominant nosological approach captures population-level variation poorly. We suggest that studying a more parsimonious case definition - impairing chronic fatigue not due to a known cause - would represent a way forward. © 2005 Cambridge University Press.

Stulemeijer M., De Jong L.W.A.M., Fiselier T.J.W., Hoogveld S.W.B., Bleijenberg G.
Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: Randomised controlled trial

2005 British Medical Journal 330 (7481); 14 – 17

<http://www.scopus.com/inward/record.url?eid=2-s2.0-11244344024&partnerID=40>

Expert Centre Chronic Fatigue, University Medical Centre Nijmegen, PO Box 9101, Nijmegen 6500 HB, Netherlands; Department of Medical Psychology, University Medical Centre Nijmegen, Nijmegen, Netherlands; Department of Paediatrics, University Medical Centre Nijmegen, Nijmegen, Netherlands

Objective: To evaluate the efficacy of cognitive behaviour therapy for adolescents aged 10-17 years with chronic fatigue syndrome. Design: Randomised controlled trial. Setting: Department of child psychology. Participants: 71 consecutively referred patients with chronic fatigue syndrome; 36 were randomly assigned to immediate cognitive behaviour therapy and 35 to the waiting list for therapy. Intervention: 10 sessions of therapy over five months. Treatment protocols depended on the type of

activity pattern (relatively active or passive). All participants were assessed again after five months. Main outcome measures: Fatigue severity (checklist individual strength), functional impairment (SF-36 physical functioning), and school attendance. Results: 62 patients had complete data at five months (29 in the immediate therapy group and 33 on the waiting list). Patients in the therapy group reported significantly greater decrease in fatigue severity (difference in decrease on checklist individual strength was 14.5, 95% confidence interval 7.4 to 21.6) and functional impairment (difference in increase on SF-36 physical functioning was 17.3, 6.2 to 28.4) and their attendance at school increased significantly (difference in increase in percentage school attendance was 18.2, 0.8 to 35.5). They also reported a significant reduction in several accompanying symptoms. Self reported improvement was largest in the therapy group. Conclusion: Cognitive behaviour therapy is an effective treatment for chronic fatigue syndrome in adolescents.

Stouten B.

Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution

2005 BMC Health Services Research 5

<http://www.scopus.com/inward/record.url?eid=2-s2.0-23044480200&partnerID=40>

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Background: A recent article by Reeves et al. on the identification and resolution of ambiguities in the 1994 chronic fatigue syndrome (CFS) research case definition recommended the Checklist Individual Strength, the Chalder Fatigue Scale, and the Krupp Fatigue Severity Scale for evaluating fatigue in CFS studies. To be able to discriminate between various levels of severe fatigue, extreme scoring on the individual items of these questionnaires must not occur too often. Methods: We derived an expression that allows us to compute a lower bound for the number of items with the maximum item score for a given study from the reported mean scale score, the number of reported subjects, and the properties of the fatigue rating scale. Several CFS studies that used the recommended fatigue rating scales were selected from literature and analyzed to verify whether abundant extreme scoring had occurred. Results: Extreme scoring occurred on a large number of the items for all three recommended fatigue rating scales across several studies. The percentage of items with the maximum score exceeded 40% in several cases. The amount of extreme scoring for a certain scale varied from one study to another, which suggests heterogeneity in the selected subjects across studies. Conclusion: Because all three instruments easily reach the extreme ends of their scales on a large number of the individual items, they do not accurately represent the severe fatigue that is characteristic for CFS. This should lead to serious questions about the validity and suitability of the Checklist Individual Strength, the Chalder Fatigue Scale, and the Krupp Fatigue Severity Scale for evaluating fatigue in CFS research. © 2005 Stouten; licensee BioMed Central Ltd.

Song S., Jason L.A.

A population-based study of chronic fatigue syndrome (CFS) experienced in differing patient groups: An effort to replicate Vercoulen et al.'s model of CFS

2005 Journal of Mental Health 14 (3); 277 – 289

<http://www.scopus.com/inward/record.url?eid=2-s2.0-22144455360&partnerID=40>

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Background: Vercoulen et al.'s (1998) model characterizes patients with chronic fatigue syndrome (CFS) as having insufficient motivation for physical activity or recovery, lacking an internal locus of control, and maintaining a self-defeating preoccupation with symptoms. However, this model has only been tested in a poorly specified group using a single comparison sample. Aims: To investigate whether Vercoulen et al.'s model provides an adequate description of CFS in a community-based

sample. Method: A community-based sample recruited through telephone interviewing (N = 28,763) produced five groups (CFS, CF-psychiatrically-explained symptoms, CF-medically-unexplained symptoms, CF-substance misuse, and idiopathic CF). The data were analysed using path analysis with the endogenous (dependent) variables, fatigue severity, physical activity, and impairment, were ratio-level measurements and consisted of at least four values. The exogenous (independent) variables except for causal attribution of fatigue were also ratio-level measurements. Results: The current investigation found that the Vercoulen et al. model adequately represented chronic fatigue secondary to psychiatric conditions but not CFS. Conclusions: This finding points to important differences between CFS and psychiatrically-explained chronic fatigue which may have an impact on the development of therapy as well as explanatory models. © Shadowfax Publishing and Taylor & Francis Group Ltd.

Shin Y.-I., Lee M.S.

Qi therapy (external qigong) for chronic fatigue syndrome: Case studies

2005 American Journal of Chinese Medicine 33 (1); 139 – 141

<http://www.scopus.com/inward/record.url?eid=2-s2.0-16344388286&partnerID=40>

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The aim of this study was to examine the effects of Qi therapy (QT) on the symptoms of chronic fatigue syndrome (CFS), including fatigue and complications. QT affected the experience of mental and emotional relaxation in the subjects of these case studies, who also gained strength to overcome their pain and fatigue. Although the results of these two case studies may not constitute conclusive evidence, they provide a foundation for the exploration of QT as a complementary therapy in the reduction of negative symptoms of chronic fatigue syndrome. © 2005 World Scientific Publishing Company.

Sevar R.

Audit of outcome in 455 consecutive patients treated with homeopathic medicines

2005 Homeopathy 94 (4); 215 - 221

<http://www.scopus.com/inward/record.url?eid=2-s2.0-26844493741&partnerID=40> 26

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This paper reports an audit of clinical outcome in 455 consecutive patients (1100 consultations) presenting for private homeopathic treatment of a chronic illness in which conventional treatment had either: failed, reached a plateau in effect, or was contra-indicated by side effects, age or condition of the patient. Three hundred and four patients (66.8%) derived benefit from homeopathic treatment. One hundred and forty-eight patients (32.5%) were able to stop or maintain a substantial reduction in their conventional drugs. The 10 most frequent clinical conditions treated were eczema, anxiety, depression, osteoarthritis, asthma, back pain, chronic cough, chronic fatigue, headaches and essential hypertension. These 195 patients constitute 43% of the total, 151 of them (77%) were improved. The success rate of treatment is similar between age ranges. There was a difference in outcome between the sexes in adults: 296 females treated, success rate 71.3%; 159 males treated, success rate 58.5%. Two patients (0.4%) had prolonged aggravation of their presenting complaints apparently attributable to homeopathic treatment. © 2005 The Faculty of Homeopathy.

Sekiya N., Shimada Y., Shintani T., Tahara E., Kouta K., Shibahara N., Terasawa K.
Reduction of perception of chronic fatigue in an observational study of patients receiving 12 weeks of Kampo therapy

2005 Journal of Alternative and Complementary Medicine 11 (5); 895 – 901

<http://www.scopus.com/inward/record.url?eid=2-s2.0-28444495860&partnerID=40>

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Objective: The aim of this study was to observe the influence of Kampo therapy on latent chronic fatigue of patients with chronic diseases. Subjects: One hundred and seventy-three (173) consecutive patients with chronic diseases came to our department for the first time. Design: This was a prospective study. Patients were divided into two groups: a chronic fatigue group (CFG) and a nonchronic fatigue group (NCFG). Based on Kampo diagnosis, both groups were prescribed Kampo formulae as an extract or decoction for 12 weeks. Outcome Measures: By using questionnaires, patients were assessed concerning their physical and mental types of fatigue, their sleep situation, and their attitude toward work or housekeeping, both before and after 12 weeks of treatment, according to Kampo diagnosis. Results: The mental fatigue, physical fatigue, and sleep scores of both groups, and the work score of CFG, were decreased. The rate of reduction of the fatigue score was significantly greater in CFG than in NCFG. The factor responsible for this difference in fatigue score was physical fatigue. Conclusions: A reduction of the perception of chronic fatigue was observed in patients receiving 12 weeks of Kampo therapy. © Mary Ann Liebert, Inc.

Saxty M., Hansen Z.

Group cognitive behavioural therapy for chronic fatigue syndrome: A pilot study

2005 Behavioural and Cognitive Psychotherapy 33 (3); 311 – 318

<http://www.scopus.com/inward/record.url?eid=2-s2.0-23144454899&partnerID=40>

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The purpose of this paper is to report a pilot of Group Cognitive Behavioural Therapy (CBT) for Chronic Fatigue Syndrome (CFS). The cognitive behavioural approach to the management of CFS has been proven effective and group therapy is often seen as a cost effective approach where possible. Six patients with CFS who met the inclusion criteria were taken from a waiting list for CBT and entered the group. Treatment involved 10 sessions of one hour spread over 18 weeks. Using questionnaire analysis, measures of pre, post, and follow-up scores were used. Analysis, comparing medians with the Wilcoxin Signed Ranks Test reached statistical significance on the Fatigue Questionnaire and the Work and Social Adjustment Scale ($p < .05$) between pre and post-treatment levels. The authors conclude that these results may represent a useful approach to the management of CFS, but that a controlled trial is now required to establish this. © 2005 British Association for Behavioural and Cognitive Psychotherapies.

Roche R., Taylor R.R.
Coping and occupational participation in chronic fatigue syndrome

2005 OTJR Occupation, Participation and Health 25 (2); 75 – 83

<http://www.scopus.com/inward/record.url?eid=2-s2.0-19944395910&partnerID=40>

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Existing studies have shown that individuals with chronic fatigue syndrome demonstrate functional impairment in several domains related to occupational participation. Researchers have not yet explored whether coping styles may be associated with occupational participation in individuals with this condition. The aim of this study was to examine the effects of coping styles on occupational participation among adults with chronic fatigue syndrome. The authors hypothesized that occupational participation would be associated with coping strategies oriented toward information seeking and maintaining activity, and that this relationship would endure despite individual differences in illness severity. The study used a cross-sectional design to describe the associations between coping and occupational participation for 47 individuals diagnosed as having chronic fatigue syndrome. Findings from linear regression analysis revealed that the coping style of maintaining activity was positively associated with occupational participation, whereas illness accommodation was negatively associated. Implications of the findings for continued research and clinical practice in occupational therapy are discussed.

Reeves W.C., Wagner D., Nisenbaum R., Jones J.F., Gurbaxani B., Solomon L., Papanicolaou D.A., Unger E.R., Vernon S.D., Heim C.

Chronic fatigue syndrome - A clinically empirical approach to its definition and study

2005 BMC Medicine 3

<http://www.scopus.com/inward/record.url?eid=2-s2.0-29544435458&partnerID=40>

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Background: The lack of standardized criteria for defining chronic fatigue syndrome (CFS) has constrained research. The objective of this study was to apply the 1994 CFS criteria by standardized reproducible criteria. Methods: This population-based case control study enrolled 227 adults identified from the population of Wichita with: (1) CFS (n=58); (2) non-fatigued controls matched to CFS on sex, race, age and body mass index (n=55); (3) persons with medically unexplained fatigue not CFS, which we term ISF (n=59); (4) CFS accompanied by melancholic depression (n=27); and (5) ISF plus melancholic depression (n=28). Participants were admitted to a hospital for two days and underwent medical history and physical examination, the Diagnostic Interview Schedule, and laboratory testing to identify medical and psychiatric conditions exclusionary for CFS. Illness classification at the time of the clinical study utilized two algorithms: (1) the same criteria as in the surveillance study; (2) a standardized clinically empirical algorithm based on quantitative assessment of the major domains of CFS (impairment, fatigue, and accompanying symptoms). Results: One hundred and sixty-four participants had no exclusionary conditions at the time of this study. Clinically empirical classification identified 43 subjects as CFS, 57 as ISF, and 64 as not ill. There was minimal association between the empirical classification and classification by the surveillance criteria. Subjects empirically classified as CFS had significantly worse impairment (evaluated by the SF-36), more severe fatigue (documented by the multidimensional fatigue inventory), more frequent and severe accompanying symptoms than those with ISF, who in turn had significantly worse scores than the not ill; this was not true for classification by the surveillance

algorithm. Conclusions: The empirical definition includes all aspects of CFS specified in the 1994 case definition and identifies persons with CFS in a precise manner that can be readily reproduced by both investigators and clinicians. © 2005 Reeves et al., licensee BioMed Central Ltd.

Rakib A., White P.D., Pinching A.J., Hedge B., Newbery N., Fakhoury W.K., Priebe S.
Subjective quality of life in patients with chronic fatigue syndrome

2005 Quality of Life Research 14 (1); 11 - 19

<http://www.scopus.com/inward/record.url?eid=2-s2.0-13844253911&partnerID=40>

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The aim of this study was to (1) assess Subjective Quality of Life (SQOL) of patients with Chronic Fatigue Syndrome (CFS) using a generic concept and to compare the findings with those in groups with mental disorders and healthy subjects, and (2) investigate whether and, if so, to what extent socio-demographic and clinical variables predict SQOL in CFS patients. Seventy-three patients diagnosed with CFS were randomly selected and interviewed from two specialised clinics. CFS was diagnosed using the Oxford Criteria. SQOL was assessed on the Manchester Short Assessment of Quality of Life (MANSA) and Health-Related Quality of Life (HRQOL) on the Medical Outcome Study Short-Form 36 (MOS) SF-36. A battery of mood and symptom questionnaires, including the Symptom Checklist Questionnaire (SCL-90-R), was administered to assess various aspects of symptomatology as potential predictor variables. Multiple regression analyses were conducted to identify predictors of SQOL. Overall, SQOL was low in CFS patients and less favourable than in groups with mental disorders and healthy subjects. Satisfaction was particularly low with life as a whole, leisure activities and financial situation. Whilst SQOL was only moderately correlated with HRQOL, the SCL-90-R score, especially SCL-90-R Depression scale score, was the best predictor of SQOL explaining 35% of the variance. HRQOL and generic SQOL appear distinct despite some overlap. The findings underline that SQOL is significantly disrupted in CFS patients. Depressive symptoms are statistically the strongest 'predictor' of SQOL, although the direction of the relationship is not established. These data suggest that treatment of depression associated with CFS, regardless of causation, could help to improve SQOL in CFS patients.

Query M., Taylor R.R.

Linkages between goal attainment and quality of life for individuals with chronic fatigue syndrome

2005 Occupational Therapy in Health Care 19 (4); 3 - 22

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33645722448&partnerID=40>

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Goal setting was the cornerstone of a rehabilitation program for people with chronic fatigue syndrome. This study examines the relationship between goal attainment and quality of life. Participants (N = 47) set goals over eight supportive and educational group sessions. Group members reported goal progress and confidence level for goal attainment. Using a forward, stepwise linear regression analysis, goal attainment emerged as the only significant predictor of quality of life improvement (B = 0.234, 95% CI for B: 0.050 to 0.419, SE = 0.091, $\hat{I}^2 = 0.372$, $p < .05$) independently of fatigue severity, symptom severity, and comorbid psychiatric diagnosis. © 2005 by The Haworth Press, Inc. All rights reserved.

Moss-Morris R., Sharon C., Tobin R., Baldi J.C.

A randomized controlled graded exercise trial for chronic fatigue syndrome: Outcomes and mechanisms of change

2005 Journal of Health Psychology 10 (2); 245 – 259

<http://www.scopus.com/inward/record.url?eid=2-s2.0-17644383290&partnerID=40>

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The aim of this study was to investigate the potential mechanisms underlying the efficacy of graded exercise therapy for chronic fatigue syndrome (CFS). Forty-nine CFS patients were randomized to a 12-week graded exercise programme or to standard medical care. At the end of treatment the exercise group rated themselves as significantly more improved and less fatigued than the control group. A decrease in symptom focusing rather than an increase in fitness mediated the treatment effect. Graded exercise appears to be an effective treatment for CFS and it operates in part by reducing the degree to which patients focus on their symptoms. Copyright © 2005 SAGE Publications.

Moss J.

Development of a functional ability scale for children and young people with myalgic encephalopathy (ME)/chronic fatigue syndrome (CFS).

2005 Journal of child health care: for professionals working with children in the hospital and community 9 (1); 20 - 30

<http://www.scopus.com/inward/record.url?eid=2-s2.0-17844376806&partnerID=40>

Association of Young People with ME, Milton Keynes MK2 2XD, UK.

The numerous symptoms and unpredictable pattern of myalgic encephalopathy (ME) make it difficult to describe, especially for children. It was left to carers to guess what the child could achieve each day, often leading to over/underestimates. A functional ability scale was needed, which measured from 0 to 100 percent able and that children and young people themselves designed. A new scale was developed from the Moss Ability Scale using the critique of 251 children and young people from the Association of Young People with ME (AYME). Responding to the shift in emphasis towards patients taking an active role in their own care, it was felt these young people would know whether the scale measured what it had set out to measure, and were asked questions on the face and content validity of the scale. There was a 99 percent agreement between the young people that the final scale was 'workable' or better.

Mears T.

Acupuncture in the treatment of post viral fatigue syndrome - A case report

2005 Acupuncture in Medicine 23 (3); 141 – 145

<http://www.scopus.com/inward/record.url?eid=2-s2.0-27244450490&partnerID=40>

This case report concerns the treatment of post viral fatigue (chronic fatigue syndrome) with electroacupuncture. This condition is particularly difficult to treat whether using conventional or complementary therapy. Whilst the treatment did not cure the patient, it appears to have facilitated her return to work and markedly improved her symptoms. There are few publications on acupuncture treatment of this condition and the approach used here has not been reported previously.

Masuda A., Kihara T., Fukudome T., Shinsato T., Minagoe S., Tei C.
The effects of repeated thermal therapy for two patients with chronic fatigue syndrome

2005 Journal of Psychosomatic Research 58 (4); 383 – 387

<http://www.scopus.com/inward/record.url?eid=2-s2.0-21344441681&partnerID=40>

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Objective: This paper describes the successful treatment of two patients with chronic fatigue syndrome (CFS) using repeated thermal therapy. Methods: Two patients with CFS underwent treatment with prednisolone (PSL), with no satisfactory effect. They were subjected to thermal therapy that consisted of a far-infrared ray dry sauna at 60°C and postsauna warming. The therapy was performed once a day, for a total of 35 sessions. After discharge, these subjects continued the therapy once or twice a week on an outpatient basis for 1 year. Results: Symptoms such as fatigue, pain, sleep disturbance, and low-grade fever were dramatically improved after 15 to 25 sessions of thermal therapy. Although PSL administration was discontinued, the subjects showed no relapse or exacerbation of symptoms during the first year after discharge. The patients became socially rehabilitated 6 months after discharge. Conclusions: These results suggest that repeated thermal therapy might be a promising method for the treatment of CFS. © 2005 Elsevier Inc. All rights reserved.

Kodama M., Kodama T.

The clinical course of interstitial pneumonia alias chronic fatigue syndrome under the control of megadose vitamin C infusion system with dehydroepiandrosterone-cortisol annex.

2005 International journal of molecular medicine 15 (1); 109 – 116

<http://www.scopus.com/inward/record.url?eid=2-s2.0-21644440462&partnerID=40>

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The year 1995 marked the onset of interstitial pneumonia spread in Nagoya, Japan. For the last 9 years, we have been accumulating clinical experience with the disease control using the combination of prophylactic use of anti-biotics and regular practice of megadose vitamin C infusion with either dehydroepiandrosterone-annex or dehydroepiandrosterone-cortisol annex. The purpose of this study is to assess the usefulness of our new treatment system for the control of interstitial pneumonia alias chronic fatigue syndrome. The results obtained are given as follows: i) The long-term maintenance of the above treatment system was effective not only for decreasing the risk for recurrence of active form pneumonia, but also for prevention of malignancy emergence in aged patients with interstitial pneumonia. ii) Evidence is presented to indicate that interstitial pneumonia was associated with increased risk for depression of which the emergence is a candidate subject causally related to the long-term use of glucocorticoid. iii) A patient with both interstitial pneumonia and depression was found to be less responsive to our treatment system. It is suggested that the use of more dehydroepiandrosterone at the sacrifice of cortisol in the infusion annex may be a choice for the control of both interstitial pneumonia and depression. iv) The description of chronic fatigue syndrome as regards the endocrinological, epidemiological and psychiatric characteristics are in good agreement with our experience on patients having interstitial pneumonia, evidence in support of our proposal that there is no convincing reasoning to separate chronic fatigue syndrome from interstitial pneumonia. v) The long-term practice of our treatment system for the control of interstitial pneumonia (an autoimmune disease) was found to suppress the inflammatory process but not the fibrotic process in the long run. vi) A few innovations were made in our treatment system to reduce the risk of bleeding or thrombosis--vascular complications of pneumonia. vii) The merit of our treatment system is to create a new hormonal environment to improve the state of immunodeficiency by use of a non-steroid substance--vitamin C which encounters little resistance from the feedback mechanism of steroid metabolism in the in vivo system.

King C., Jason L.A.

Improving the diagnostic criteria and procedures for chronic fatigue syndrome

2005 Biological Psychology 68 (2); 87 - 106

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4644240574&partnerID=40>

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Since the publication of the case definition for chronic fatigue syndrome (CFS) in 1988 the diagnostic criteria have been revised twice in the U.S. None of the case definitions were derived empirically. As a result, there is concern regarding the sensitivity, specificity, and reliability of the criteria. The goal of the present study was to identify methods for improving the diagnostic criteria for CFS. Three groups of 15 participants each were recruited: participants with (1) CFS, (2) major depressive disorder (MDD), and (3) healthy controls. Using statistical procedures, three methods for improving the diagnostic criteria were explored: identification of new diagnostic symptoms, the use of severity ratings for symptomatology, and the identification of standardized measures that differentiate cases of CFS from other conditions. Results of the present study suggest that these three methods hold promise for improving the sensitivity, specificity, and reliability of the diagnostic criteria for CFS. © 2004 Published by Elsevier B.V.

Hutchings A., Raine R., Sanderson C., Black N.

An experimental study of determinants of the extent of disagreement within clinical guideline development groups

2005 Quality and Safety in Health Care 14 (4); 240 – 245

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Objective: To assess the effect of design features and clinical and social cues on the extent of disagreement among participants in a formal consensus development process. Methods: Factorial design involving 16 groups consisting of 135 general practitioners (GPs) and 42 mental health professionals from England. The groups rated the appropriateness of four mental health interventions for three conditions (chronic back pain, irritable bowel syndrome, and chronic fatigue syndrome) in the context of various clinical and social cues. The groups differed in three design features: provision of a systematic literature review (versus not provided), group composition (mixed versus GP only), and assumptions about the healthcare resources available (realistic versus idealistic). Disagreement was measured using the mean absolute deviation from a group's median rating for a scenario. Results: None of the design features significantly affected the extent of disagreement within groups (all $p > 0.3$). Disagreement did differ between treatments (closer consensus for cognitive behavioural therapy and behavioural therapy than for brief psychodynamic intervention therapy and antidepressants) and cues (closer consensus for depressed patients and patients willing to try any treatment). Conclusion: In terms of the extent of disagreement in the groups in this study, formal consensus development was a robust technique in that the results were not dependent on the way it was conducted.

Hamilton W.T., Gallagher A.M., Thomas J.M., White P.D.

The prognosis of different fatigue diagnostic labels: A longitudinal survey

2005 Family Practice 22 (4); 383 - 388

<http://www.scopus.com/inward/record.url?eid=2-s2.0-27144559467&partnerID=40>

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Background. Several different diagnostic labels exist for the fatigue syndromes, including chronic fatigue syndrome (CFS), myalgic encephalomyelitis (ME) and postviral fatigue syndrome (PVFS). An allied condition is fibromyalgia. No study has examined prognostic differences across these different labels. **Objective.** To compare the prognoses of patients labelled with different fatigue syndromes in primary care. **Methods.** We performed a longitudinal survey, using electronic records from the General Practice Research Database. All 18 122 patients diagnosed by their GP with a fatigue syndrome from 1988-2001 with a minimum of one year of records after diagnosis were collated into four groups: CFS, ME, PVFS and fibromyalgia. CFS and ME were combined for the main analysis as no code for CFS was available until 1995. The length of illness was calculated as the interval between the diagnosis and the last recorded fatigue symptom, expressed as days per year, to account for differing lengths of record after diagnosis. **Results.** Patients with CFS/ME combined had a worse prognosis (median length of illness 80 days per year; interquartile range 0-242) than fibromyalgia (51; 0-244) or PVFS 0 (0-108), a significant difference, $P < 0.001$. In a subgroup analysis, ME had a worse prognosis (median length of illness in days per year 106; interquartile range 0-259) than CFS (33; 0-170), $P < 0.001$, in spite of a better course before diagnosis. Secondary outcome measures were consistent with these results. **Conclusion.** There were important differences in outcome between the various fatigue labels, with ME having the worst prognosis and PVFS the best. This could be an adverse effect of the label ME itself. Alternatively, patients who are destined to have a worse prognosis may preferentially attract the ME label. Our data support the first interpretation. © The Author (2005). Published by Oxford University Press. All rights reserved.

Haines D.R., Wang M., Campion P.D., Alladin W.

Are patients with chronic widespread pain and/or fatigue placebo responders? An evaluation employing a randomised crossover trial of proglumide

2005 Pain Clinic 17 (1); 1 - 13

<http://www.scopus.com/inward/record.url?eid=2-s2.0-17144412975&partnerID=40>

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Proglumide is a cholecystokinin antagonist which has been shown to block placebo hyperalgesia in human patients. In contrast to the placebo response, the placebo phenomenon involves negative expectations such as fearing the worst. We hypothesised that patients with chronic 'widespread' conditions, such as fibromyalgia and chronic fatigue syndrome, were so hampered by fearful appraisals of their current state that they might in fact be placebo responders. If so, proglumide should counteract the situation and at least improve some aspect these patients' lives. However, a randomised double blind crossover trial of proglumide versus ascorbic acid in patients with chronic pain and/or fatigue did not support this hypothesis, there being no clinically significant improvements during the proglumide phase of the trial. Analysis of the changes in the fearful

appraisal subscale scores of the PASS questionnaire during the control phase of the trial, showed that some of the patients could be divided into placebo and nocebo responders; i.e. the fearful appraisal reduced during a placebo response in the control phase of the trial, but increased during a nocebo response. The proglumide phase of the trial showed the expected reduction in fearful appraisal in the nocebo responders, but the placebo response was diminished by the proglumide, i.e. the fearful appraisal scores increased in the placebo responders. It seems that the proglumide exerts paradoxical effects on fearful appraisal, tending to return both placebo and nocebo responses towards pretrial baseline values. These responses were not strong enough to show a clinical effect in the trial, but do indicate a possible interaction of proglumide with fearful appraisal. Some of the implications of this finding are discussed. © 2005 VSP.

Gaitanis P., Tooley G., Edwards B.

Physical activity, emotional stress, sleep disturbances, and daily fluctuations in chronic fatigue symptomatology

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<http://www.scopus.com/inward/record.url?eid=2-s2.0-27844537336&partnerID=40>

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The current study explored the relationships between physical and emotional stress and the symptomatology of chronic fatigue syndrome (CFS). Fifty-four CFS patients were studied using a longitudinal design. A self-report format was used to collect daily measures of major physical (sleep disturbance and physical activity) and emotional (subjective emotional stress level) Stressors, as well as measures of levels of fatigue and secondary symptoms. The variables accounted for a moderate variance at the individual and occasion levels. Sleep disturbance and emotional stress were found to be positively associated with levels of fatigue and symptomatology, whereas physical activity was found to have a negative relationship with fatigue only. The severity of fatigue and symptoms were found to fluctuate daily in relation with the variables, indicating the complex nature of the associations. Copyright © 2005 by Bellwether Publishing, Ltd. All rights reserved.

Fowler T., Duthie P., Thapar A., Farmer A.

The definition of disabling fatigue in children and adolescents

2005 BMC Family Practice 6

<http://www.scopus.com/inward/record.url?eid=2-s2.0-24044471320&partnerID=40>

Department of Psychological Medicine, Wales College of Medicine, Cardiff University, United Kingdom; Brynffynnon Child and Family Service Unit, Pontypridd, United Kingdom; MRC Social, Genetic, Developmental Psychiatric Research Centre, Institute of Psychiatry, London, United Kingdom

Background: Disabling fatigue is the main illness related reason for prolonged absence from school. Although there are accepted criteria for diagnosing chronic fatigue in adults, it remains uncertain as to how best to define disabling fatigue and Chronic Fatigue Syndrome (CFS) in children and adolescents. In this population-based study, the aim was to identify children who had experienced an episode of disabling fatigue and examine the clinical and demographic differences between those individuals who fulfilled a narrow definition of disabling fatigue and those who fulfilled broader definitions of disabling fatigue. Methods: Participants (aged 8-17 years) were identified from a population-based twin register. Parent report was used to identify children who had ever experienced a period of disabling fatigue. Standardised telephone interviews were then conducted with the parents of these affected children. Data on clinical and demographic characteristics, including age of onset, gender, days per week affected, hours per day spent resting, absence from school, comorbidity with depression and a global measure of impairment due to the fatigue, were

examined. A narrow definition was defined as a minimum of 6 months disabling fatigue plus at least 4 associated symptoms, which is comparable to the operational criteria for CFS in adults. Broader definitions included those with at least 3 months of disabling fatigue and 4 or more of the associated symptoms and those with simply a minimum of 3 months of disabling fatigue. Groups were mutually exclusive. Results: Questionnaires were returned by 1468 families (65% response rate) and telephone interviews were completed on 99 of the 129 participants (77%) who had experienced fatigue. There were no significant differences in demographic and clinical characteristics or levels of impairment between those who fulfilled the narrower definition and those who fulfilled the broader definitions. The only exception was the reported number of days per week that the child was affected by the fatigue. All groups demonstrated evidence of substantial impairment associated with the fatigue. Conclusion: Children and adolescents who do not fulfil the current narrow definition of CFS but do suffer from disabling fatigue show comparable and substantial impairment. In primary care settings, a broader definition of disabling fatigue would improve the identification of impaired children and adolescents who require support. © 2005 Fowler et al; licensee BioMed Central Ltd.

Darbishire L., Seed P., Ridsdale L.

Predictors of outcome following treatment for chronic fatigue

2005 British Journal of Psychiatry 186 (APR.); 350 – 351

<http://www.scopus.com/inward/record.url?eid=2-s2.0-17144415541&partnerID=40>

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We explored the role of baseline characteristics of 105 patients who presented with fatigue in primary care in determining outcome following either graded exercise or cognitive-behavioural therapy. Meeting the criteria for chronic fatigue syndrome was the most powerful predictor of poor outcome and this negative effect was enhanced by greater functional impairment or greater perceived negative consequences, but was not further enhanced by both.

Chumpitaz B.R., Nazir S., Patel Y., Bergen M.T.

Computer automated experimentation for the control and assessment of the classically conditioned eye blink response

2005 Bioengineering, Proceedings of the Northeast Conference 265; 266

<http://www.scopus.com/inward/record.url?eid=2-s2.0-28444432254&partnerID=40>

The classically conditioned eye blink experiment provides another way to study associative learning. This type of associative learning has many important features which are helpful in neurological studies such as Parkinson's disease, Alzheimer's disease, and chronic fatigue syndrome. Our goal was to design a portable medical device for East Orange, Veteran Affairs Medical Center, which collects Electromyogram, Electrocardiogram and Respiration signals from a human subject for biomedical research studies. The major priorities of this project were to reduce power consumption, person's safety, increase portability and to use the latest technologies for the device. Lab View 6.0 was used for this system which collects data from the subject and transferred it to the computer. Hardware components for this system provide acoustic signals, air puff to eye for blinking, and detect condition physiological signals. © 2005 IEEE.

Bowen J., Pheby D., Charlett A., McNulty C.
Chronic Fatigue Syndrome: A survey of GPs' attitudes and knowledge

2005 Family Practice 22 (4); 389 - 393

<http://www.scopus.com/inward/record.url?eid=2-s2.0-27144488333&partnerID=40>

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Background. GPs need evidence and guidance to help them diagnose and manage Chronic Fatigue Syndrome (CFS)/ME appropriately. **Objectives.** The aim of this survey was to obtain baseline data and identify the factors associated with GPs' attitudes to and knowledge of CFS/ME. The attitude of GPs to the condition is an important indicator of likely prognosis. **Methods.** A postal questionnaire was sent to 1054 GPs served by Taunton, Bristol and Gloucester laboratories. GPs' attitudes to nine statements about CFS/ME were assessed and the factors associated with positive or negative responses were determined. Knowledge of the clinical features was also assessed. **Results.** 811 GPs (77%) returned the questionnaire. 48% of GPs did not feel confident with making a diagnosis of CFS/ME and 41% did not feel confident in treatment. 72% of GPs accepted CFS/ME as a recognisable clinical entity and those GPs had significantly more positive attitudes. Three other key factors that were significantly, positively associated with GPs' attitudes were knowing someone socially with CFS/ME, being male and seeing more patients with the condition in the last year. **Conclusion.** Despite the publication of guidance for GPs on CFS/ME, confidence with making a diagnosis and management was found to be low. Educational initiatives and guidance for GPs should stress the importance of accepting CFS/ME as a recognisable clinical entity, as this is linked to having a positive attitude and could lead to improved confidence to make a diagnosis and treat CFS/ME patients. © The Author (2005). Published by Oxford University Press. All rights reserved.

Bentler S.E., Hartz A.J., Kuhn E.M.
Prospective observational study of treatments for unexplained chronic fatigue

2005 Journal of Clinical Psychiatry 66 (5); 625 - 632

<http://www.scopus.com/inward/record.url?eid=2-s2.0-19544370367&partnerID=40>

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Background: Unexplained chronic fatigue is a frequent complaint in primary care. A prospective observational study design was used to evaluate whether certain commonly used therapies for unexplained chronic fatigue may be effective. **Method:** Subjects with unexplained chronic fatigue of unknown etiology for at least 6 months were recruited from the Wisconsin Chronic Fatigue Syndrome Association, primary care clinics, and community chronic fatigue syndrome presentations. The primary outcome measure was change in a 5-question fatigue score from 6 months to 2 years. Self-reported interventions tested included prescribed medications, non-prescribed supplements and herbs, lifestyle changes, alternative therapies, and psychological support. Linear regression analysis was used to test the association of each therapy with the outcome measure after adjusting for statistically significant prognostic factors. **Results:** 155 subjects provided information on fatigue and treatments at baseline and follow-up. Of these subjects, 87% were female and 79% were middle-aged. The median duration of fatigue was 6.7 years. The percentage of users who found a treatment helpful was greatest for coenzyme Q10 (69% of 13 subjects), dehydroepiandrosterone (DHEA) (65% of 17 subjects), and ginseng (56% of 18 subjects). Treatments at 6 months that predicted subsequent fatigue improvement were vitamins ($p = .08$), vigorous exercise ($p = .09$), and yoga ($p = .002$). Magnesium ($p = .002$) and support groups ($p = .06$) were strongly associated with fatigue worsening from 6 months to 2 years. Yoga appeared to be most effective for subjects who did not

have unclear thinking associated with the fatigue. Conclusion: Certain alternative therapies for unexplained chronic fatigue, especially yoga, deserve testing in randomized controlled trials.

Bazelmans E., Prins J.B., Lulofs R., Van Der Meer J.W.M., Bleijenberg G.
Cognitive behaviour group therapy for chronic fatigue syndrome: A non-randomised waiting list controlled study

2005 *Psychotherapy and Psychosomatics* 74 (4); 218 – 224

<http://www.scopus.com/inward/record.url?eid=2-s2.0-20844443132&partnerID=40>

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Background: It has been demonstrated that individual cognitive behaviour therapy is an effective treatment for chronic fatigue syndrome (CFS). The aim of the present study was to investigate the effectiveness of cognitive behaviour group therapy (CBGT) in an unselected group of CFS patients. Additionally, pretreatment characteristics of CFS patients who improve after CBGT were explored. Methods: In a non-randomised waiting list controlled design, 31 patients were allocated to CBGT and 36 to the waiting list condition. CBGT consisted of 12 two-hour sessions during 6 months. Main outcome measures were fatigue (Checklist Individual Strength) and functional impairment (Sickness Impact Profile). Results: A moderate effect on fatigue in favour of CBGT was found. For functional impairment, the effect was opposite to what was expected. Patients who improved after CBGT had less complaints at baseline compared to patients who did not improve. Conclusions: An explanation for the moderate effect might be that during CBGT, rest and relaxation were too much emphasised. Furthermore, an unselected group of CFS patients and therapists inexperienced in CB(G)T for CFS participated. Suggestions to improve CBGT for future research are given. Copyright © 2005 S. Karger AG.

Barlow J.H., Wright C.C., Turner A.P., Bancroft G.V.
A 12-month follow-up study of self-management training for people with chronic disease: Are changes maintained over time?

2005 *British Journal of Health Psychology* 10 (4); 589 – 599

<http://www.scopus.com/inward/record.url?eid=2-s2.0-27644468413&partnerID=40>

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Objective. A previous study reported some improved outcomes at 4-month follow-up after attendance on a lay-led, chronic disease self-management course (CDSMC). The purpose of this study was to determine whether changes were maintained over time (i.e. at 12 months) and to describe participants' current use of self-management techniques. Design. The study was a 12-month follow-up of a sample of 171 participants who attended a CDSMC in the UK. Method. Data were collected by self-administered questionnaires mailed to participants 12 months after they commenced a CDSMC and via telephone interviews with a sub-sample. Results. The sample had a mean age of 54 years, mean disease duration of 16 years, 73% were women, and chronic diseases included endometriosis, depression, diabetes, myalgic encephalomyelitis, osteoporosis and polio. The significant improvements in outcomes identified at 4 months (i.e. cognitive symptom management, self-efficacy, communication with physician, fatigue, anxious and depressed moods and health distress) were sustained at 12 months. No significant changes between 4- and 12-month

assessments were found on any study variables. Interview data confirmed that participants continued to use some of the self-management techniques learned on the course. Conclusion. Attendance on the CDSMC may lead to longer-term changes in key outcomes such as self-efficacy, use of some self-management behaviours and some aspects of health status (e.g. fatigue, depressed mood). © 2005 The British Psychological Society.

Wittkowski A., Toye K., Richards H.L.

A cognitive behaviour therapy group for patients with chronic fatigue syndrome: A preliminary investigation

2004 Behavioural and Cognitive Psychotherapy 32 (1); 107 – 112

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1242307908&partnerID=40>

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A number of studies suggest that individual cognitive-behavioural therapy (CBT) is beneficial to patients suffering from Chronic Fatigue Syndrome (CFS). This study investigated the effectiveness of group CBT in reducing fatigue and distress in five outpatients with a diagnosis of CFS throughout therapy and at 3-month follow-up. The nature of the group, treatment outcomes and benefits of this approach are outlined. Group CBT was acceptable to participants and led to improvements in fatigue as well as cognitive functioning.

Whiteley P., Shattock P., Todd L., Wright A.

Correlates of overlapping fatigue syndromes

2004 Journal of Nutritional and Environmental Medicine 14 (3); 247 – 259

<http://www.scopus.com/inward/record.url?eid=2-s2.0-11844297772&partnerID=40>

Autism Research Unit, Sch. of Hlth., Nat. and Social Sci., University of Sunderland, Bolton, United Kingdom

Purpose: To identify significant behavioural and somatic symptoms associated with formal receipt of a chronic fatigue syndrome diagnosis. Design: Retrospective cross-sectional analysis of patient self-report questionnaires held on a computerized database. Materials and Methods: Analysis of self-report responses to a questionnaire from patients referred from a UK clinic specializing in the diagnosis and treatment of fatigue disorders (n=371), 259 of whom were formally diagnosed either exclusively or combinatorially with fatigue diagnoses of myalgic encephalomyelitis, chronic fatigue syndrome and fibromyalgia. Results: Non-parametric (chi-squared) analysis showed that 17 response items (current and historical behaviour all somatic variables) were significantly associated with patients formally diagnosed with fatigue disorders (p<0.01). Conclusions: The presence of current and historical variables outside of the traditional diagnostic framework of fatigue syndromes provides preliminary evidence for a redefinition of exclusive overlapping fatigue syndromes into a more general spectral model.

Weatherley-Jones E., Nicholl J.P., Thomas K.J., Parry G.J., McKendrick M.W., Green S.T., Stanley P.J., Lynch S.P.J.

A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome

2004 Journal of Psychosomatic Research 56 (2); 189 – 197

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1542298138&partnerID=40>

Medical Care Research Unit, Sch. of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA, United Kingdom; Communicable Diseases Directorate, Royal Hallamshire Hospital, Sheffield, United Kingdom; Seacroft Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; St. James's University Hospital, University of Leeds, Beckett Street, Leeds, United Kingdom

Objective: There is no management regime for chronic fatigue syndrome (CFS) that has been found to be universally beneficial and no treatment can be considered a "cure" [1]. Patients with CFS may use complementary and alternative medicine (CAM) [1]. Our aim was to evaluate homeopathic treatment in reducing subjective symptoms of CFS. **Method:** Using a triple-blind design (patient and homeopath blind to group assignment and data analyst blind to group until after initial analyses to reduce the possibility of bias due to data analyst), we randomly assigned patients to homeopathic medicine or identical placebo. One hundred and three patients meeting the Oxford criteria for CFS were recruited from two specialist hospital out patient departments. Patients had monthly consultations with a professional homeopath for 6 months. Main outcome measures were scores on the subscales of the Multidimensional Fatigue Inventory (MFI) and proportions of each group attaining clinically significant improvements on each subscale. Secondary outcome measures were the Fatigue Impact Scale (FIS) and the Functional Limitations Profile (FLP). Ninety-two patients completed treatment in the trial (47 homeopathic treatment, 45 placebo). Eighty-six patients returned fully or partially completed posttreatment outcome measures (41 homeopathic treatment group who completed treatment, 2 homeopathic treatment group who did not complete treatment, 38 placebo group who completed treatment, and 5 placebo group who did not complete treatment). **Results:** Seventeen of 103 patients withdrew from treatment or were lost to follow-up. Patients in the homeopathic medicine group showed significantly more improvement on the MFI general fatigue subscale (one of the primary outcome measures) and the FLP physical subscale but not on other subscales. Although group differences were not statistically significant on four out of the five MFI subscales (the primary outcome measures), more people in the homeopathic medicine group showed clinically significant improvement. More people in the homeopathic medicine group showed clinical improvement on all primary outcomes (relative risk=2.75, P=.09). **Conclusions:** There is weak but equivocal evidence that the effects of homeopathic medicine are superior to placebo. Results also suggest that there may be nonspecific benefits from the homeopathic consultation. Further studies are needed to determine whether these differences hold in larger samples. © 2004 Elsevier Inc. All rights reserved.

Wallman K.E., Morton A.R., Goodman C., Grove R., Guilfoyle A.M.

Randomised controlled trial of graded exercise in chronic fatigue syndrome

2004 Medical Journal of Australia 180 (9); 444 – 448

<http://www.scopus.com/inward/record.url?eid=2-s2.0-2442586726&partnerID=40>

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Objective: To investigate whether 12 weeks of graded exercises with pacing would improve specific physiological, psychological and cognitive functions in people with chronic fatigue syndrome (CFS) **Design:** Randomised controlled trial. **Setting:** Human performance laboratory at the University of Western Australia. **Participants:** 61 patients aged between 16 and 74 years diagnosed with CFS. **Interventions:** Either graded exercise with pacing (32 patients) or relaxation/flexibility therapy (29 patients) performed twice a day over 12 weeks. **Main outcome measures:** Changes in any of the

physiological, psychological or cognitive variables assessed. Results: Following the graded exercise intervention, scores were improved for resting systolic blood pressure ($P= 0.018$), work capacity ($W\dot{A}\cdot kg^{-1}$) ($P= 0.019$), net blood lactate production ($P= 0.036$), depression ($P= 0.027$) and performance on a modified Stroop Colour Word test ($P= 0.029$). Rating of perceived exertion scores, associated with an exercise test, was lower after graded exercise ($P= 0.013$). No such changes were observed in the relaxation/flexibility condition, which served as an attention-placebo control. Conclusions: Graded exercise was associated with improvements in physical work capacity, as well as in specific psychological and cognitive variables. Improvements may be associated with the abandonment of avoidance behaviours.

Viner R., Gregorowski A., Wine C., Bladen M., Fisher D., Miller M., El Neil S.
Outpatient rehabilitative treatment of chronic fatigue syndrome (CFS/ME)

2004 Archives of Disease in Childhood 89 (7); 615 – 619

<http://www.scopus.com/inward/record.url?eid=2-s2.0-3042807880&partnerID=40>

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Aims: To assess the outcome of outpatient multidisciplinary rehabilitative treatment (graded activities/exercise programme, family sessions, and supportive care) compared with supportive care alone for children and adolescents with chronic fatigue syndrome (CFS/ME). Methods: Fifty six young people (aged 9-17 years) with CFS/ME by standard criteria were followed up for 3-24 months. All subjects received supportive care. Families additionally opted to either enter the rehabilitation programme (supportive care plus graded activities/exercise programme and family sessions) or have no additional treatment. Results: Twenty two (39%) subjects had supportive care alone and 26 (46%) entered the programme. Treatment groups were comparable at baseline in terms of age, severity and duration of illness, Wellness score, and school attendance. At end of follow up, those in the programme group had significantly higher Wellness score and school attendance than those having supportive care alone. The programme significantly reduced the overall severity of illness: after the programme, 43% had complete resolution of CFS/ME compared to only 4.5% of those having supportive care alone. The presence of depressed mood and family beliefs about the aetiology of CFS/ME were not significantly associated with outcomes. Conclusions: Outpatient rehabilitative treatment offers significant potential to improve the prognosis of CFS/ME in childhood and adolescence.

Vermeulen R.C.W., Scholte H.R.

Exploratory Open Label, Randomized Study of Acetyl- and Propionylcarnitine in Chronic Fatigue Syndrome

2004 Psychosomatic Medicine 66 (2); 276 - 282

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1642413119&partnerID=40>

Research Center Amsterdam, Amsterdam, Netherlands; CFS Research Center Amsterdam, Waalstraat 25, Amsterdam, 1078 BR, Netherlands

Objectives: We compared the effects of acetylcarnitine, propionycarnitine and both compounds on the symptoms of chronic fatigue syndrome (CFS). Methods: In an open, randomized fashion we compared 2 g/d acetyl-L-carnitine, 2 g/d propionyl-L-carnitine, and its combination in 3 groups of 30 CFS patients during 24 weeks. Effects were rated by clinical global impression of change. Secondary endpoints were the Multidimensional Fatigue Inventory, McGill Pain Questionnaire, and the Stroop attention concentration test. Scores were assessed 8 weeks before treatment; at randomization; after 8, 16, and 24 weeks of treatment; and 2 weeks later. Results: Clinical global impression of change after treatment showed considerable improvement in 59% of the patients in the acetylcarnitine group and 63% in the propionycarnitine group, but less in the acetylcarnitine plus

propionycarnitine group (37%). Acetylcarnitine significantly improved mental fatigue ($p = .015$) and propionylcarnitine improved general fatigue ($p = .004$). Attention concentration improved in all groups, whereas pain complaints did not decrease in any group. Two weeks after treatment, worsening of fatigue was experienced by 52%, 50%, and 37% in the acetylcarnitine, propionylcarnitine, and combined group, respectively. In the acetylcarnitine group, but not in the other groups, the changes in plasma carnitine levels correlated with clinical improvement. Conclusions: Acetylcarnitine and propionylcarnitine showed beneficial effect on fatigue and attention concentration. Less improvement was found by the combined treatment. Acetylcarnitine had main effect on mental fatigue and propionylcarnitine on general fatigue.

Van Hoof E., Coomans D., Cluydts R., De Meirleir K.
The Fennell phase inventory in a belgian sample

2004 Journal of Chronic Fatigue Syndrome 12 (1); 53 – 69

<http://www.scopus.com/inward/record.url?eid=2-s2.0-10044231870&partnerID=40>

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The present study is a follow-up of the research conducted by Jason, Fennell et al. (1995, 1999, 2000) on a multistage theory for chronic fatigue syndrome (CFS). This multistage model is a very promising method for the evaluation of patients suffering from CFS and could facilitate the appropriate selection of various psychosocial therapies that improve the patient's ability to cope with their illness. Four predictive factors emerged with moderate to excellent reliability. A Spearman's rank correlation revealed positive correlations between our four-factor model and the three-factor model identified by Jason et al. (1999). A correlation matrix between the dimensional psychological investigation and the Fennell Phases revealed characteristics as suggested by previous research. Biological parameters varied over the different phases suggesting an important interaction between body and psyche. © 2004 by The Haworth Press, Inc. All rights reserved.

Vallings R.
Hypnosis in the management of chronic fatigue syndrome

2004 Journal of Chronic Fatigue Syndrome 12 (4); 37 – 46

<http://www.scopus.com/inward/record.url?eid=2-s2.0-30044445509&partnerID=40> 140

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During the past 30 years hypnosis has become recognised as a useful adjunct to traditional medical therapies, and has become part of mainstream medicine. Hypnosis societies provide training for health professionals to obtain registrable qualifications. The modality has been incorporated in the management of many medical conditions and diseases, with opportunities for symptom control, building confidence and enhancing the benefits of regular therapies. There are many opportunities for using hypnosis as an adjunctive therapy in the management of Chronic Fatigue Syndrome, despite some early difficulties. Problems likely to be encountered are discussed and the structure of the hypnosis session is outlined. Suggestions are given for practitioners to construct useful scripts, which can be used to teach self-hypnosis. © 2004 by The Haworth Press, Inc. All rights reserved.

Turkington D., Hedwat D., Rider I., Young A.H.
Recovery from chronic fatigue syndrome with modafinil

2004 Human Psychopharmacology 19 (1); 63 – 64

<http://www.scopus.com/inward/record.url?eid=2-s2.0-0742289911&partnerID=40>

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[No abstract available]

Tritt K., Nickel M., Mitterlehner F., Nickel C., Forthuber P., Leiberich P., Rother W., Loew T.
Chronic fatigue and indicators of long-term employment disability in psychosomatic inpatients

2004 Wiener Klinische Wochenschrift 116 (05-Jun); 182 – 189

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1842784946&partnerID=40>

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The major goal of this study was to determine indicators of long-term disability for psychosomatic inpatients with chronic fatigue syndrome. To this end, a cross-sectional study was performed with a random sample of patients (n=1000, response rate: 83.9%) at a psychosomatic inpatient clinic. 51.1% of the patients (n=429) reported intensely persistent exhaustion that had no logical relation to actual exertion. 159 (37.1%) patients in this group were disabled from working and these comprised the main target group of this study. Significantly more patients in the target group worked part time, were disabled for a disproportionately long period of time (50.9% of all were disabled for more than 6 months in the previous year), and felt stressed because of conflicts with their superiors and/or colleagues (in each case, $P < 0.01$). While more frequent psychological comorbidity was not found, they reported physical complaints more often. It was not the patients fit for work who felt more burdened with chronic fatigue, but rather the employment-disabled, who were actually exposed to fewer demands. These patients had, in comparison with those fit to work, a stronger fixation on somatic complaints, inadequate perception of physical and psychic sensations, difficulties getting along with other people and in coping with a regular job (in each case, $P < 0.01$). Prospective examination of these indicators could help detect predictor variables for long-term disability in chronic fatigue. Such predictors could contribute to timely social-medical assessment and treatment.

Taylor R.R.
Quality of life and symptom severity for individuals with chronic fatigue syndrome: Findings from a randomized clinical trial

2004 American Journal of Occupational Therapy 58 (1); 35 – 43

<http://www.scopus.com/inward/record.url?eid=2-s2.0-2142643139&partnerID=40>

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OBJECTIVE. Chronic fatigue syndrome is a profoundly disabling condition characterized by severe, unrelenting fatigue and a number of other physical and cognitive symptoms. Currently, there is no cure or widely accepted treatment for chronic fatigue syndrome, and few rehabilitation programs exist to address quality of life issues in chronic fatigue syndrome. In the present randomized clinical trial, the effects of an integrative, consumer-driven rehabilitation program on quality of life and symptom severity for individuals with chronic fatigue syndrome were examined. **METHOD.** Forty-seven participants were randomly assigned to either an immediate program group (n = 23) or a

delayed program control group (n = 24) and assessed with the Chronic Fatigue Syndrome Symptom Rating Scale and the Quality of Life Index before the program, after program participants completed the group phase, and after program participants completed the one-on-one phase. It was hypothesized that the program would lead to improvements in quality of life and an overall reduction in symptom severity. RESULTS. Linear growth models were estimated comparing program and control conditions over time using random-effects regression analyses. Significant condition by time interactions were observed for the main outcomes of symptom severity and overall quality of life. Effect sizes for these interactions involving symptom severity (Cohen's d = 0.71) and overall quality of life (Cohen's d = .66) were moderate. CONCLUSIONS. Findings indicate that consumer driven programs such as this one can have a positive impact on symptom severity and quality of life over time for individuals with chronic fatigue syndrome.

Solomon L., Reeves W.C.

Factors influencing the diagnosis of chronic fatigue syndrome

2004 Archives of Internal Medicine 164 (20); 2241 – 2245

<http://www.scopus.com/inward/record.url?eid=2-s2.0-7544243047&partnerID=40>

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Background: Most of what is believed about chronic fatigue syndrome (CFS) is based on clinic-based studies. These studies may not reflect CFS cases in the population. Methods: We used data from a population-based study of CFS to identify factors associated with receiving a CFS diagnosis. Wichita, Kan, residents were screened by random-digit dialing. Eligible individuals completed a telephone interview. Respondents meeting CFS criteria were invited for a clinical evaluation to confirm CFS. We analyzed all persons with confirmed CFS. The main outcomes of this study, prevalence and incidence of CFS, are published elsewhere. Herein, we present an exploratory analysis with previous CFS diagnosis as the outcome, predicted by demographic and symptom characteristics. Results: We confirmed CFS in 90 subjects; 14 (16%) had been previously diagnosed as having CFS. Persons in the middle- vs the higher-income group were more likely to have been diagnosed as having CFS (9 [29%] of 31 subjects vs 3 [8%] of 39 subjects; $P=.03$), as were those with sudden vs gradual fatigue onset (7 [41%] of 17 subjects vs 4 [6%] of 64 subjects; $P < .01$), those reporting tender lymph nodes (7 [33%] of 21 subjects vs 7 [10%] of 69 subjects; $P=.02$), and those reporting a sore throat (6 [35%] of 17 subjects vs 8 [11%] of 73 subjects; $P=.02$). Only 17 (21%) of 81 subjects had sudden fatigue onset, and tender lymph nodes (reported in 21 [23%] of 90 subjects) and a sore throat (reported in 17 [19%] of 90 subjects) were the least common symptoms. Conclusion: Most cases of CFS in the population are unrecognized by the medical community; persons diagnosed as having CFS may be different from persons with CFS in the general population.

Severens J.L., Prins J.B., van der Wilt G.J., van der Meer J.W.M., Bleijenberg G.

Cost-effectiveness of cognitive behaviour therapy for patients with chronic fatigue syndrome

2004 QJM - Monthly Journal of the Association of Physicians 97 (3); 153 – 161

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1542709225&partnerID=40>

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Background: There is some evidence that cognitive behaviour therapy (CBT) is efficacious in chronic fatigue syndrome (CFS), but little data on its cost-effectiveness. Design: Prospective economic analysis alongside a randomized clinical trial. Methods: CFS patients were randomly assigned to

CBT, guided support groups (SG), or the 'natural course' (NC, no protocol-based interventions). Patients were treated for 8 months and followed-up for another 6 months. Costs per patient showing clinically significant improvement, based on the CIS fatigue scale, and costs per quality-adjusted life year, were determined for a time period of 14 months. Results: Data were available for 171 patients at 8 months and for 128 at 14 months. At 8 and 14 months, the percentages of improved patients were 31% and 27% for CBT, 9% and 11% for SG, and 12% and 20% for NC. Mean QALYs gained at 14 months were, for CBT, SG and NC, respectively, 0.0737, -0.0018 and 0.0458. CBT and SG mean treatment costs were \$1,490 and \$424. Other medical costs for CBT, SG, and NC, respectively, were \$324, \$623 and \$412 for the first period, and \$232, \$561 and \$378 for the second period. Non-medical costs for these periods for CBT, SG and NC were \$262, \$550, \$427 and \$226, \$439, \$287, respectively. Productivity costs were considerable, but not significantly different between groups. Discussion: CBT was less costly and more effective than SG. Compared to NC, the baseline incremental cost-effectiveness of CBT was \$20,516 per CFS patient showing clinically significant improvement, and \$21,375 per QALY. The bootstrap ratios showed considerable uncertainty regarding the results. Future research should focus on productivity costs, and follow patients prospectively over a longer period. © Association of Physicians 2004; all rights reserved.

Santaella M.L., Font I., Disdier O.M.

Comparison of oral nicotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome.

2004 Puerto Rico health sciences journal 23 (2); 89 – 93

<http://www.scopus.com/inward/record.url?eid=2-s2.0-5444224804&partnerID=40>

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OBJECTIVE: To compare effectiveness of oral therapy with reduced nicotinamide adenine dinucleotide (NADH) to conventional modalities of treatment in patients with chronic fatigue syndrome (CFS). **BACKGROUND:** CFS is a potentially disabling condition of unknown etiology. Although its clinical presentation is associated to a myriad of symptoms, fatigue is a universal and essential finding for its diagnosis. No therapeutic regimen has proven effective for this condition. **METHODS:** A total of 31 patients fulfilling the Centers for Disease Control criteria for CFS, were randomly assigned to either NADH or nutritional supplements and psychological therapy for 24 months. A thorough medical history, physical examination and completion of a questionnaire on the severity of fatigue and other symptoms were performed each trimester of therapy. In addition, all of them underwent evaluation in terms of immunological parameters and viral antibody titers. Statistical analysis was applied to the demographic data, as well as to symptoms scores at baseline and at each trimester of therapy. **RESULTS:** The twelve patients who received NADH had a dramatic and statistically significant reduction of the mean symptom score in the first trimester ($p < 0.001$). However, symptom scores in the subsequent trimesters of therapy were similar in both treatment groups. Elevated IgG and Ig E antibody levels were found in a significant number of patients. **CONCLUSIONS:** Observed effectiveness of NADH over conventional treatment in the first trimester of the trial and the trend of improvement of that modality in the subsequent trimesters should be further assessed in a larger patient sample.

Ryan M., Gevirtz R.

Biofeedback-based psychophysiological treatment in a primary care setting: An initial feasibility study

2004 *Applied Psychophysiology Biofeedback* 29 (2); 79 – 93

<http://www.scopus.com/inward/record.url?eid=2-s2.0-3242742919&partnerID=40>

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We sought to determine whether an intervention labeled "biofeedback" could be implemented with patients who were diagnosed with "functional" disorders (Irritable Bowel Syndrome, Fibromyalgia/Chronic Fatigue Syndrome, Myofascial Pain, Anxiety with somatic features, or Noncardiac Chest Pain), in a primary care setting, and whether cost savings through lowered utilization of medical services would be realized. Seventy patients were initially randomized into a treatment group or comparison group based on willingness to participate. Ultimately, 19 patients completed treatment and 30 were followed through usual treatment as a comparison. Treatment patients completed symptom diaries while working with a biofeedback therapist in the primary care facility. Both groups' medical expenses were tracked for 6 months prior to and 6 months after the treatment time interval. Patients in the treatment group lowered symptom frequency and severity significantly. Medical costs were differentially reduced in this group such that all costs were \$72 less in the treatment group and \$9 in the comparison for the 6 months following the treatment time period. ($p < .001$). Unfortunately, a large group of assigned treatment patients did not start or complete treatment. These patients had high initial costs and went up even higher post. No comparable group could be found among the controls, limiting any inference regarding cost/benefit. Biofeedback based interventions for "functional" disorders can be easily integrated into primary care settings, can reduce symptoms, and may be able to reduce overall medical costs in this group of patients known as heavy utilizers.

Ridsdale L., Darbishire L., Seed P.T.

Is graded exercise better than cognitive behaviour therapy for fatigue? A UK randomized trial in primary care

2004 *Psychological Medicine* 34 (1); 37 - 49

<http://www.scopus.com/inward/record.url?eid=2-s2.0-0942288048&partnerID=40>

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Background. Patients frequently present with unexplained fatigue in primary care, but there have been few treatment trials in this context. We aimed to test cognitive behaviour therapy (CBT) and graded exercise therapy (GET) for patients presenting to their family doctor with fatigue. Secondly, we described the outcome for a cohort of patients who presented to the same doctors with fatigue, who received standard care, plus a booklet. **Method.** This was a randomized trial, followed by a prospective cohort study. Twenty-two practices in SE England referred 144 patients aged 16 to 75 years with over 3 months of unexplained fatigue. Self-rated fatigue score, the hospital anxiety and depression rating scale, functional impairment, physical step-test performance and causal attributions were measured. In the trial six sessions of CBT or GET were randomly allocated. **Results.** In the therapy groups the mean fatigue score decreased by 10 points (95% confidence interval (CI) = - 25 to - 15), with no significant difference between groups (mean difference = - 1.3; CI = - 3.9 to 1.3). Fewer patients attended for GET. At outcome one-half of patients had clinically important fatigue in both randomized groups, but patients in the group offered CBT were less anxious. Twenty-seven per cent of the patients met criteria for CFS at baseline. Only 25% of this subgroup recovered, compared to 60% of the subgroup that did not meet criteria for CFS. **Conclusions.** Short courses of GET were not superior to CBT for patients consulting with fatigue of over 3 months in primary care. CBT was easier 'to sell'. Low recovery in the CFS subgroup suggests that brief treatment is too short.

Reynolds K.J., Vernon S.D., Bouchery E., Reeves W.C.
The economic impact of chronic fatigue syndrome

2004 Cost Effectiveness and Resource Allocation 2

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4243049230&partnerID=40>

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Background: Chronic fatigue syndrome (CFS) is a chronic incapacitating illness that affects between 400,000 and 800,000 Americans. Despite the disabling nature of this illness, scant research has addressed the economic impact of CFS either on those affected or on the national economy. Methods: We used microsimulation methods to analyze data from a surveillance study of CFS in Wichita, Kansas, and derive estimates of productivity losses due to CFS. Results. We estimated a 37% decline in household productivity and a 54% reduction in labor force productivity among people with CFS. The annual total value of lost productivity in the United States was \$9.1 billion, which represents about \$20,000 per person with CFS or approximately one-half of the household and labor force productivity of the average person with this syndrome. Conclusion. Lost productivity due to CFS was substantial both on an individual basis and relative to national estimates for other major illnesses. CFS resulted in a national productivity loss comparable to such losses from diseases of the digestive, immune and nervous systems, and from skin disorders. The extent of the burden indicates that continued research to determine the cause and potential therapies for CFS could provide substantial benefit both for individual patients and for the nation. © 2004 Reynolds et al; licensee BioMed Central Ltd.

Puri B.K.

The use of eicosapentaenoic acid in the treatment of chronic fatigue syndrome

2004 Prostaglandins Leukotrienes and Essential Fatty Acids 70 (4); 399 – 401

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1842453648&partnerID=40>

Imaging Sciences Department, Imperial College School of Medicine, Hammersmith Hospital, Du Cane Road, London W12 0HS, United Kingdom There is evidence that there is an association between chronic fatigue syndrome, a condition of unknown aetiology, and essential fatty acids. This evidence is based on the actions of essential fatty acids, the results of proton neurospectroscopy studies, and essential fatty acid trial data. A series of patients with chronic fatigue syndrome were treated solely with a high-eicosapentaenoic acid-containing essential fatty acid supplement. All showed improvement in their symptomatology within eight to 12 weeks. These results, which are consistent with a recent detailed report of cerebral and clinical changes associated with a high intake of eicosapentaenoic acid, suggest that this n-3 highly unsaturated fatty acid may offer the hope of effective treatment for at least some patients with chronic fatigue syndrome. © 2004 Elsevier Ltd. All rights reserved.

Powell P., Bentall R.P., Nye F.J., Edwards R.H.T.

Patient education to encourage graded exercise in chronic fatigue syndrome: 2-Year follow-up of randomised controlled trial

2004 British Journal of Psychiatry 184 (FEB.); 142 – 146

<http://www.scopus.com/inward/record.url?eid=2-s2.0-0442307620&partnerID=40>

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Background: An earlier trial demonstrated good outcomes after 1 year for patients with chronic fatigue syndrome (CFS) who received an educational intervention designed to encourage graded activity. Aims: To determine 2-year outcomes for the same treated patients and the response to

treatment of patients formerly in the control condition. Method: Patients in the treatment groups (n=114) were followed up at 2 years; 32 patients from the control group were offered the intervention after 1 year and were assessed 1 year later. Assessments were the self-rated measures used in the original trial. Results: At 2 years 63 of the treated patients (55%) no longer fulfilled trial criteria for CFS compared with 64 patients (56%) at 1 year. Fourteen of 30 crossover patients (47%) achieved a good outcome at 1 year and seven (23%) no longer fulfilled criteria for CFS. Conclusions: Benefits of the intervention were maintained at 2 years. Delaying treatment is associated with reduced efficacy and required more intensive therapy.

Nisenbaum R., Reyes M., Unger E.R., Reeves W.C.
Factor analysis of symptoms among subjects with unexplained chronic fatigue: What can we learn about chronic fatigue syndrome?

2004 Journal of Psychosomatic Research 56 (2); 171 – 178

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1542298143&partnerID=40>

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Objective: Chronic fatigue syndrome (CFS) case definitions agree that fatigue must be unexplained, debilitating and present for at least 6 months, but they differ over accompanying symptoms. Our objective was to compare the 1994 CFS case-defining symptoms with those identified by factor analysis. Methods: We surveyed the Wichita population and measured the occurrence of 21 symptoms in 1391 chronically fatigued subjects who did not report fatigue-associated medical or psychiatric conditions. We used factor analyses to identify symptom dimensions of fatigue and cluster analysis to assign subjects to subgroups. Results: Forty-three subjects had CFS. We confirmed three factors: musculoskeletal, infection and cognition-mood-sleep, essentially defined by CFS symptoms. Although factor scores were higher among CFS subjects, CFS and non-CFS distributions overlapped substantially. Three clusters also showed overlap between CFS and non-CFS subjects. Conclusion: CFS symptomatology is a multidimensional phenomenon overlapping with other unexplained fatiguing syndromes and this must be considered in CFS research. © 2004 Elsevier Inc. All rights reserved.

Nijs J., Cloostermans B., McGregor N., Vaes P., DeMeirleir K.
Construct validity and internal consistency of the chronic fatigue syndrome activities and participation questionnaire (CFS-APQ)

2004 Physiotherapy Theory and Practice 20 (1); 31 – 40

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1842710123&partnerID=40>

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Identifying patients' activity limitations is crucial for teaching Chronic Fatigue Syndrome (CFS) patients to effectively manage their activity level. Therefore, a questionnaire to assess activity limitations/participation restrictions in CFS patients was recently constructed. In this study, the internal consistency, the discriminant validity, and the convergent validity of this measure, named the CFS-Activities and Participation Questionnaire (CFS-APQ), were investigated. Convergent and discriminant validity are considered two fundamental aspects of construct validity. An envelope containing the CFS-APQ and the Medical Outcomes Short Form 36 Health Status Survey (SF-36) was sent to 149 CFS patients. Eighty-eight out of 149 CFS patients (59.1%) filled in and returned the questionnaires. Cronbach's Alpha reliability coefficients were >0.87. The CFS-APQ total scores

correlated statistically significant with six out eight SF-36 subscales (bodily functioning, physical role functioning, bodily pain, general health perception, vitality and social functioning), with Spearman Rank correlation coefficients ranging from -0.34 to -0.78. The highest correlation coefficients were obtained between the CFS-APQ total scores and the subscales 'physical functioning' and 'social functioning', no significant correlations were observed with the SF-36 subscales emotional role functioning and mental health. In conclusion, the items of the Dutch version of the CFS-APQ have been found to have good internal consistency, and these results substantiate both the convergent and the discriminant validity of the scores obtained with this questionnaire.

Naschitz J.E., Rozenbaum M., Shaviv N., Fields M.C., Enis S., Babich J.P., Manor H., Yeshurun D., Sabo E., Rosner I.

The feeling of fatigue - Fatigue severity by unidimensional versus composite questionnaires

2004 Behavioral Medicine 29 (4); 167 - 172

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4143152777&partnerID=40>

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The authors' purpose in this study was to compare the perception of fatigue severity as measured by different fatigue questionnaires. The authors evaluated 3 groups of patients in a cross-sectional study: chronic fatigue syndrome (CFS, n = 20), non-CFS fatigue (n = 20), and familial Mediterranean fever (FMF, n = 25). In addition, the authors tracked 7 patients with CFS longitudinally for severity of fatigue. The severity of fatigue-related symptoms was assessed with 2 questionnaires: the unidimensional Chalder's Fatigue Severity Scale (CH) and the composite Fatigue Impact Scale (FI) which has 3 subscales-cognitive, physical, and social-and a total score. In the cross-sectional study, correlations between CH and FI cognitive scores were $r = .78$ ($p < .0001$), CH versus FI physical scores $r = .603$ ($p < .0001$), CH versus FI social scores $r = .66$ ($p < .0001$), and CH versus FI total scores $r = .74$ ($p < .0001$). In the longitudinal survey of CFS patients, the authors compared 30 questionnaires revealing correlations of CH versus FI cognitive scores $r = .64$ ($p = .0004$), CH versus FI physical $r = .68$ ($p = .0001$), CH versus FI social $r = .87$ ($p < .0001$), and CH versus FI total $r = .90$ ($p < .0001$). Fatigue severity as assessed by the unidimensional CH scale and the composite FI scale is comparable. The simple CH scale may be adequate for the assessment of the feeling of fatigue, in general, and for monitoring the severity of fatigue in CFS, in particular.

McDermott C., Richards S.C.M., Ankers S., Selby M., Harmer J., Moran C.J.

An evaluation of a chronic fatigue lifestyle management programme focusing on the outcome of return to work or training

2004 British Journal of Occupational Therapy 67 (6); 269 – 273

<http://www.scopus.com/inward/record.url?eid=2-s2.0-3042855894&partnerID=40>

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This articles presents the results of an audit of clinical outcomes from an occupation therapist led service for patients with chronic fatigue syndrome (CFS). The service offers group outpatient lifestyle management sessions, in which patients are encouraged to restructure lifestyle patterns in order to facilitate improvements in fatigue and function. The cohort studied consisted of 98 consecutive patient attending the service who fulfilled the 1994 Centers for Disease Control criteria for CFS. The median illness duration was 5 years. The treatment offered consisted of six group sessions in lifestyle management together with three additional review sessions. The primary outcome measure was a return by the patient to employment, voluntary work or training. The cohort was followed up at a median of 18 months using a self-report questionnaire. Among the treated

patient, 42% (31/74 reported new part-time or full-time employment, voluntary work or training. The results of this study suggest that a lifestyle management programme offered by an occupational therapist led specialist service may provide positive outcomes, in terms of a return by patients to work and training, and indicates the need for a randomised controlled trial to provide definitive evidence of this.

McCrone P., Ridsdale L., Darbishire L., Seed P.
Cost-effectiveness of cognitive behavioural therapy, graded exercise and usual care for patients with chronic fatigue in primary care

2004 Psychological Medicine 34 (6); 991 - 999

<http://www.scopus.com/inward/record.url?eid=2-s2.0-0942276100&partnerID=40>

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Background. Chronic fatigue is a common condition, frequently presenting in primary care. The aim of this study was to compare the cost-effectiveness of cognitive behavioural therapy (CBT) and graded exercise therapy (GET), and to compare therapy with usual care plus a self-help booklet (BUC). Method. Patients drawn from general practices in South East England were randomized to CBT or GET. The therapy groups were then compared to a group receiving BUC recruited after the randomized phase. The main outcome measure was clinically significant improvements in fatigue. Cost-effectiveness was assessed using the net-benefit approach and cost-effectiveness acceptability curves. Results. Costs were available for 132 patients, and cost-effectiveness results for 130. Costs were dominated by informal care. There were no significant outcome or cost differences between the therapy groups. The combined therapy group had significantly better outcomes than the standard care group, and costs that were on average £149 higher (a non-significant difference). Therapy would have an 81.9% chance of being cost-effective if society were willing to attach a value of around £500 to each four-point improvement in fatigue. Conclusion. The cost-effectiveness of cognitive behavioural therapy and graded exercise were similar unless higher values were placed on outcomes, in which case CBT showed improved cost-effectiveness. The cost of providing therapy is higher than usual GP care plus a self-help booklet, but the outcome is better. The strength of this evidence is limited by the use of a non-randomized comparison. The cost-effectiveness of therapy depends on how much society values reductions in fatigue. © 2004 Cambridge University Press.

Kennedy G., Abbot N.C., Spe.nce V., Underwood C., Belch J.J.F.
The Specificity of the CDC-1994 criteria for chronic fatigue syndrome: Comparison of health status in three groups of patients who fulfill the criteria

2004 Annals of Epidemiology 14 (2); 95 - 100

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1242270604&partnerID=40>

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PURPOSE: The Centers for Disease Control (CDC)-1994 definition of chronic fatigue syndrome (CFS) is very broad, and there have been suggestions that it lacks specificity. To test this, we have compared three groups of patients, all of whom fulfill the criteria but self-report different etiologies. METHODS: Patients with self-reported symptoms which developed sporadically (sCFS, n=48); after

Gulf War service (GW, n=24); and following exposure to organophosphate insecticides (OP, n=25) underwent a clinical examination, completed the MOS SF-36 quality of life and Hospital Anxiety and Depression scales, and were assessed for major and minor criteria for CDC-1994 CFS. RESULTS: Significant differences in simple clinical measures and outcome measures were observed between groups. The GW group had significantly more severe physical symptoms - fatigue, muscle and multi-joint pain - than OP or sCFS, and the sCFS group was significantly less impaired than the other two groups in terms of role emotional and mental health. In all three groups, a majority of patients exhibited muscle weakness in the lower limbs, and significant numbers of patients had absent or abnormal reflexes. CONCLUSIONS: Differences in simple, easily performed clinical outcome measurements can be observed between groups of patients, all of whom fulfill the CDC-1994 criteria for CFS. It is likely that their response to treatment may also vary. The specificity of the CFS case definition should be improved to define more homogeneous groups of patients for the purposes of treatment and research. © 2004 Elsevier Inc. All rights reserved.

Jason L.A., Torres-Harding S.R., Jurgens A., Helgerson J.
Comparing the Fukuda et al. criteria and the Canadian case definition for chronic fatigue syndrome
2004 Journal of Chronic Fatigue Syndrome 12 (1); 37 – 52
<http://www.scopus.com/inward/record.url?eid=2-s2.0-10044278290&partnerID=40>

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Because the pathogenesis of Chronic Fatigue Syndrome (CFS) has yet to be determined, case definitions have relied on clinical observation in classifying signs and symptoms for diagnosis. The selection of diagnostic signs and symptoms has major implications for which individuals are diagnosed with CFS and how seriously the illness is viewed by health care providers, disability insurers and rehabilitation planners, and patients and their families and friends. Diagnostic criteria also have implications for whether research based on varying definitions can be synthesized. The current investigation examined differences between CFS as defined by Fukuda et al. (1994) and a set of criteria that has been proposed for a clinical Canadian Case definition. There were twenty-three participants who met the Canadian criteria, 12 in the CFS (Fukuda et al. (7) criteria) group and the 33 from the chronic fatigue (CF)-psychiatric group. Dependent measures included: work status, psychiatric comorbidity, symptoms, and functional impairment (measured by the Medical Outcomes Study). People meeting the Fukuda et al. and Canadian criteria were compared with people who had a chronically fatiguing illness explained by a psychiatric condition. Statistical tests used included binomial logistic regression and analysis of variance. The Canadian criteria group, in contrast to the Fukuda et al. criteria group, had more variables that statistically significantly differentiated them from the psychiatric comparison group. Overall, there were 17 symptom differences between the Canadian and CF-psychiatric group, but only 7 symptom differences between the CFS and CF-psychiatric group. The findings suggest that both the Canadian and Fukuda et al. case definitions select individuals who are statistically significantly different from psychiatric controls with chronic fatigue, with the Canadian criteria selecting cases with less psychiatric comorbidity, more physical functional impairment, and more fatigue/weakness, neuropsychiatric, and neurological symptoms. © 2004 by The Haworth Press, Inc. All rights reserved.

Huibers M.J.H., Kant I.J., Knottnerus J.A., Bleijenberg G., Swaen G.M.H., Kasl S.V.
Development of the chronic fatigue syndrome in severely fatigued employees: Predictors of outcome in the Maastricht cohort study

2004 Journal of Epidemiology and Community Health 58 (10); 877 – 882

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4644238425&partnerID=40>

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Study objective: To identify risk factors of the development of the chronic fatigue syndrome (CFS), the persistence or recurrence of fatigue, or recovery from fatigue in a large sample of fatigued employees. Design: Analyses were based on the Maastricht cohort study (MCS), a prospective population based cohort study among more than 12 000 employees. Multiple regression models were used to identify predictors of CFS-like caseness (meeting research criteria for CFS), non-CFS fatigue caseness, or no fatigue caseness. Setting: The working population in the Netherlands. Participants: 1143 employees with medically unexplained fatigue were followed up prospectively for 44 months. Main results: At 44 month follow up, 8% of the employees were CFS-like cases (none of who reported to have received a CFS diagnosis), 40% were non-CFS fatigue cases, and 52% were no longer fatigue cases. Factors that predicted CFS-like caseness compared with non-CFS fatigue caseness were high age, exhaustion, female sex, low education, and visits to the general practitioner. Factors that predicted CFS-like caseness compared with no fatigue caseness were fatigue, exhaustion, low education, visits to the GP and occupational physician, and bad self rated health. Factors that predicted non-CFS fatigue caseness compared with no fatigue caseness were fatigue, low self perceived activity, exhaustion, anxious mood, and bad self rated health. Conclusions: Unexplained fatigue among employees in some instances is a precursor of the development of CFS. The prognostic role of self rated health suggests that prevention and treatment of chronic fatigue should be aimed at changing the perception of health or illness. Less clear is the role of health care seeking or receiving a CFS diagnosis.

Huibers M.J.H., Bleijenberg G., Van Amelsvoort L.G.P.M., Beurskens A.J.H.M., Van Schayck C.P., Bazelmans E., Knottnerus J.A.

Predictors of outcome in fatigued employees on sick leave: Results from a randomised trial

2004 Journal of Psychosomatic Research 57 (5); 443 – 449

<http://www.scopus.com/inward/record.url?eid=2-s2.0-9644289452&partnerID=40>

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The main objective of this study was to identify predictors of fatigue caseness, work resumption and chronic fatigue syndrome (CFS)-like caseness in a sample of fatigued employees on sick leave. For 12 months, 151 fatigued employees on sick leave, 44% of whom met research criteria for CFS at baseline, were followed. Measures included fatigue, health aspects, psychological problems, burnout, causal attributions and self-efficacy. Logistic regression analysis was used to determine associations between predictor variables at baseline and outcome at follow-up. After 12 months, 43% of the patients were no longer fatigue cases, and 62% had resumed work. Recovery from fatigue caseness was predicted by stronger psychological attributions and other perception-related factors, whereas work resumption was predicted by lower age, male sex, CFS-like caseness and less cognitive difficulties. Lower physical functioning scores were predictive of (the development of) CFS-like caseness. Recovering from persistent fatigue and work resumption seem to result from different

underlying processes and do not necessarily fall together. As many factors associated with outcome in fatigue reflect illness perception, the prevention of persistent fatigue and CFS may partly be achieved by the modification of perception. © 2004 Elsevier Inc. All rights reserved.

Hartz A.J., Bentler S., Noyes R., Hoehns J., Logemann C., Sinift S., Butani Y., Wang W., Brake K., Ernst M., Kautzman H.

Randomized controlled trial of Siberian ginseng for chronic fatigue

2004 Psychological Medicine 34 (1); 51 - 61

<http://www.scopus.com/inward/record.url?eid=2-s2.0-9144220786&partnerID=40>

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Background. Chronic fatigue greatly affects quality of life and is a common reason for consulting a physician. Since conventional therapy is often of limited help, fatigued patients may use herbal treatments. This randomized controlled trial evaluated the effectiveness of Siberian ginseng. **Method.** Subjects were recruited from advertisements in Iowa (82%) and members of chronic fatigue syndrome support groups (18%). Potential subjects were required to have substantial fatigue \geq 6 months with no identifiable cause. The mean change in a fatigue measure was compared for placebo and Siberian ginseng at 1 and 2 months. Comparisons were for all subjects and for subjects with characteristics previously identified in the literature as important for categorizing chronic fatigue. **Results.** Ninety-six subjects were randomized to treatment groups, and 76 provided information at 2 months of follow-up. Fatigue among subjects assigned to either placebo or Siberian ginseng was substantially reduced during the study, but differences between treatment groups were not statistically significant in the full sample. Fatigue severity and duration had a statistically significant interaction with response to Siberian ginseng at the $P < 0.05$ level. Treatment was effective at 2 months for 45 subjects with less severe fatigue ($P = 0.04$ unadjusted for multiple comparisons). and for 41 subjects with fatigue for \geq 5 years ($P = 0.09$ unadjusted for multiple comparisons). **Conclusion.** Overall efficacy was not demonstrated. However, the findings of possible efficacy for patients with moderate fatigue suggests that further research may be of value.

Gill A.C., Dosen A., Ziegler J.B.

Chronic Fatigue Syndrome in Adolescents: A Follow-up Study

2004 Archives of Pediatrics and Adolescent Medicine 158 (3); 225 – 229

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1442264775&partnerID=40>

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Objectives: To compare the frequency of persistent symptoms up to 8 years after illness onset in adolescents diagnosed as having chronic fatigue syndrome, idiopathic chronic fatigue, and unexplained fatigue for less than 6 months, and to determine if hospital admission is associated with outcome. **Design:** A cohort study using questionnaire follow-up. **Setting:** A tertiary referral hospital. **Patients:** Consecutive adolescents referred for assessment of persistent fatigue were identified and retrospectively divided into 3 groups according to the diagnostic criteria for chronic fatigue syndrome and idiopathic chronic fatigue. **Intervention:** A questionnaire was designed and administered by telephone at a mean of 4.57 years after the initial examination. **Main Outcome Measure:** The persistence of self-reported symptoms was compared with respect to patient group and admission. **Results:** Outcome data were obtained for 34 (69%) of the 49 eligible subjects. Twenty-five percent of the chronic fatigue syndrome group showed near to complete improvement, 31% showed partial improvement, and 44% showed no improvement. The idiopathic chronic fatigue

group had near to complete recovery in 50%, partial in 10%, and no improvement in 40%. Those with unexplained fatigue for less than 6 months had all recovered. There was no difference between the outcome of the subjects admitted to the hospital and those managed as outpatients. Conclusions: Adolescents with less than 6 months of fatigue have a good outcome. Unexplained fatigue lasting more than 6 months has a similar outcome regardless of the presence of minor criteria for chronic fatigue syndrome.

Garraalda M.E., Rangel L.

Impairment and coping in children and adolescents with chronic fatigue syndrome: A comparative study with other paediatric disorders

2004 Journal of Child Psychology and Psychiatry and Allied Disciplines 45 (3); 543 – 552

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1642366662&partnerID=40>

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Background: Functional impairment is a key feature of chronic fatigue syndrome (CFS) of childhood. Aim: To compare impairment, illness attitudes and coping mechanisms in childhood CFS and in other paediatric disorders. Method: Participants were 28 children and adolescents with CFS, 30 with juvenile idiopathic arthritis (JIA) and 27 with emotional disorders (ED). The measures used were interviews with children and parents, with detailed enquiry on impairment, including the Functional Disability Inventory (FDI), Illness Attitudes Scales (IAS), and Kidcope to measure coping styles in relation to common problems, illness and disability. Results: Children with CFS reported significantly more illness impairment, especially in school attendance, than those with JIA and ED. They had higher 'worry about illness' scores on the IAS. On the Kidcope they named school issues (work, expectations, attendance) as illness- or disability-related problems more than the other two groups. Fewer CFS participants reported using problem solving as a strategy to cope with illness and disability than with other problems in their lives. More in the CFS than in the JIA group used emotional regulation to cope with illness and disability. Fewer in the CFS than in the ED groups used social withdrawal to cope with illness and self-criticism for disability, but more used resignation to cope with disability. Conclusion: Severe illness-related impairment, particularly through school non-attendance, and high levels of illness-related school concerns appear specific to CFS. CFS may also have characteristically high levels of generalised illness worry and particular styles of coping with illness and disability. © Association for Child Psychology and Psychiatry, 2004.

Gallagher A.M., Thomas J.M., Hamilton W.T., White P.D.

Incidence of fatigue symptoms and diagnoses presenting in UK primary care from 1990 to 2001

2004 Journal of the Royal Society of Medicine 97 (12); 571 – 575

<http://www.scopus.com/inward/record.url?eid=2-s2.0-10644254770&partnerID=40>

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Little is known about whether the incidence of symptoms of fatigue presented in primary care, and the consequent diagnoses made, change over time. The UK General Practice Research Database was used to investigate the annual incidence of both fatigue symptoms and diagnoses recorded in UK primary care from 1990 to 2001. The overall incidence of all fatigue diagnoses decreased from 87 per 100 000 patients in 1990 to 49 in 2001, a reduction of 44%, while postviral fatigue syndromes decreased from 81% of all fatigue diagnoses in 1990 to 60% in 2001. Chronic fatigue syndrome (CFS) and myalgic encephalomyelitis (ME) together increased from 9% to 26% of all fatigue diagnoses. The incidence of fibromyalgia increased from less than 1 per 100 000 to 35 per 100 000. In contrast, there was no consistent change in the incidence of all recorded symptoms of fatigue,

with an average of 1503 per 100000, equivalent to 1.5% per year. CFS/ME and fibromyalgia were rarely diagnosed in children and were uncommon in the elderly. All symptoms and diagnoses were more common in females than in males. The overall incidence of fatigue diagnoses in general has fallen, but the incidence rates of the specific diagnoses of CFS/ME and fibromyalgia have risen, against a background of little change in symptom reporting. This is likely to reflect fashions in diagnostic labelling rather than true changes in incidence.

Busichio K., Tiersky L.A., Deluca J., Natelson B.H.
Neuropsychological deficits in patients with chronic fatigue syndrome

2004 Journal of the International Neuropsychological Society 10 (2); 278 – 285
<http://www.scopus.com/inward/record.url?eid=2-s2.0-1842590574&partnerID=40>

Chronic Fatigue Syndrome Center, Newark, NJ, United States; Fairleigh Dickinson University, School of Psychology, 1000 River Road, Teaneck, NJ 07666, United States; Department of Neurosciences, UMDNJ-New Jersey Medical School, Newark, NJ, United States; Kessler Medical Research, Rehabilitation/Education Corporation, West Orange, NJ, United States; Dept. of Phys. Med./Rehabilitation, UMDNJ-New Jersey Medical School, Newark, NJ, United States

The degree of neuropsychological dysfunction across multiple domains was examined in individuals suffering from chronic fatigue syndrome (CFS). In this descriptive study, a similar series of neuropsychological tests was administered to a group of CFS patients and healthy participants. More specifically, CFS patients (n = 141) who met the 1994 Case Definition criteria were compared to 76 healthy control participants on tests of memory, attention (concentration), speed of information processing, motor speed, and executive functioning. On the 18 measures administered, CFS patients scored 1 standard deviation below the healthy mean on nine measures and scored 2 standard deviations below the healthy mean on four of the measures. Moreover, results indicated that CFS patients were more likely than healthy controls to fail (1.6 SD below the healthy mean) at least one test in each of the following domains: attention, speed of information processing, and motor speed, but not on measures of memory and executive functioning. Finally, CFS patients demonstrated a greater total number of tests failed across domains. Copyright © 2004 INS. Published by Cambridge University Press.

Blacker C.V.R., Greenwood D.T., Wesnes K.A., Wilson R., Woodward C., Howe I., Ali T.
Effect of galantamine hydrobromide in chronic fatigue syndrome: A randomized controlled trial

2004 Journal of the American Medical Association 292 (10); 1195 – 1204
<http://www.scopus.com/inward/record.url?eid=2-s2.0-4444247418&partnerID=40>

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Context: There is no established pharmacological treatment for the core symptoms of chronic fatigue syndrome (CFS). Galantamine hydrobromide, an acetyl cholesterone inhibitor, has pharmacological properties that might benefit patients with CFS. Objective: To compare the efficacy and tolerability of galantamine hydrobromide in patients with CFS. Design, Setting, and Patients: Randomized, double-blind trial conducted June 1997 through July 1999 at 35 outpatient centers in the United Kingdom (n = 17), United States (n = 14), the Netherlands (n = 2), Sweden (n = 1), and Belgium (n = 1) involving 434 patients with a clinical diagnosis of CFS (modified US Centers for Disease Control and Prevention criteria). Interventions: A total of 89 patients were randomly assigned to receive 2.5 mg of galantamine hydrobromide; 86 patients, 5.0 mg; 91 patients, 7.5 mg; and, 86 patients, 10 mg (these patients received medicine in the tablet form 3 times per day); a

total of 82 patients received matching placebo tablets 3 times per day. Main Outcome Measures: The primary efficacy variable was the global change on the Clinician Global Impression Scale after 4, 8, 12, and 16 weeks of treatment. Secondary outcomes were changes in core symptoms of CFS on the Chalder Fatigue Rating Scale, the Fibromyalgia Impact Questionnaire, and the Pittsburgh Sleep Quality Index; changes in quality of life on the Nottingham Health Profile; and assessment of plasma-free cortisol levels and cognitive performance on a computer-based battery of tests. Results: After 16 weeks, there were no statistically significant differences between any of the galantamine or placebo groups in clinical condition on the Clinician Global Impression Scale, or for any of the secondary end points. Exploratory regression analysis failed to detect any consistent prognostic factor that might have influenced the primary or any secondary outcome measures. Conclusion: This trial did not demonstrate any benefit of galantamine over placebo in the treatment of patients with CFS.

Bazelmans E., Prins J.B., Hoogveld S., Bleijenberg G.
Manual-based cognitive behaviour therapy for chronic fatigue syndrome: Therapists' adherence and perceptions

2004 Cognitive Behaviour Therapy 33 (3); 143 – 150

<http://www.scopus.com/inward/record.url?eid=2-s2.0-4544266387&partnerID=40>

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Several randomized controlled trials have indicated that cognitive behaviour therapy is an effective treatment for chronic fatigue syndrome. In 1 of these studies 13 therapists applied cognitive behaviour therapy for chronic fatigue syndrome in 83 chronic fatigue syndrome patients. In the present study therapists' adherence and perceptions of the manual are studied. Following completion of the study the therapists were asked to complete a questionnaire. Audiotaped sessions were conducted to verify the therapists' adherence. Analyses of the audiotapes showed that in 87% of the sessions this appeared to be the case. The questionnaire revealed that the therapists found it more difficult to treat patients with chronic fatigue syndrome than to treat patients with psychological or other physical problems. Treatment aspects posing the most problems were integrating individual problems into the standardized treatment, dealing with the patients' lack of confidence in the treatment and handling insufficient motivation. © 2004 Taylor & Francis.

Van Hoof E., Coomans D., Cluydts R., De Meirleir K.
Association between Fennell Phase Inventory scores and immune and RNase-L parameters in chronic fatigue syndrome

2004 Journal of Chronic Fatigue Syndrome 12 (2); 19 – 34

<http://www.scopus.com/inward/record.url?eid=2-s2.0-22844451726&partnerID=40>

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All patients suffering from a chronic condition, are challenged to manage the reality of their disease, the accompanying anxiety, the problems of daily living, and the effect on relationships. Therefore, when confronted with debilitating complaints, patients suffering from chronic fatigue syndrome (CFS) need to adapt to a new way of living during the course of their illness. Fennell developed an integrated model to manage CFS. This article is a follow-up of a study by Jason et al. (9, 10) to verify the existence of the different phases. Although not all differences are statistically significant, a

clear distinction is made according to the conclusions drawn by Jason et al. (9, 10). Relationships between these distinctions and measures of symptoms, disability, psychological distress, coping, and immune parameters were revealed using non-parametric statistical tests. © 2004 by The Haworth Press, Inc. All rights reserved.

Jason L., Benton M., Torres-Harding S., Muldowney K.

The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS

Patient Education and Counseling

<http://www.scopus.com/inward/record.url?eid=2-s2.0-63549114856&partnerID=40>

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Objective: The energy envelope postulates that patients with Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS) will improve functioning when maintaining expended energy levels at the same level as available energy level. Methods: Estimated weekly Energy Quotients were established by dividing expended energy level by perceived energy level and multiplying by 100. Two groups of patients were identified following participation in a non-pharmacologic intervention trial. Some were able to keep expended energy close to available energy and others were not successful at this task. Results: Those who were able to stay within their energy envelope had significant improvements in physical functioning and fatigue severity. Conclusion: Findings suggest that helping patients with ME/CFS maintain appropriate energy expenditures in coordination with available energy reserves can help improve functioning over time. Practice implications: Health care professionals that treat patients with ME/CFS might incorporate strategies that help patients self-monitor and self-regulate energy expenditures. © 2009 Elsevier Ireland Ltd. All rights reserved.

Goudsmit E.M., Ho-Yen D.O., Dancy C.P.

Learning to cope with chronic illness. Efficacy of a multi-component treatment for people with chronic fatigue syndrome

Patient Education and Counseling

<http://www.scopus.com/inward/record.url?eid=2-s2.0-67649410594&partnerID=40>

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Objective: The aim of this study was to determine the efficacy of an out-patient, multi-component programme developed for patients with chronic fatigue syndrome (CFS). Methods: Twenty-two patients were assessed before and after six months of treatment. Findings were compared with 22 individuals on the waiting list. The programme offered medical care as well as information and counselling to help patients to understand, accept and cope with their illness. Results: At six months, there were significant differences between the groups for fatigue, self-efficacy and anxiety. Overall, 82% of the treated patients reported feeling better and 23% had improved to such a degree that they were discharged from the clinic. The gains were maintained at twelve months. Conclusion: This programme was found to be both helpful and acceptable and may provide a useful first-line intervention for many patients with CFS. Practice implications: Short, pragmatic programmes may be as effective as cognitive-behaviour therapy. © 2009 Elsevier Ireland Ltd. All rights reserved.

Other

Sakudo A., Kuratsune H., Kato Y.H., Ikuta K.

Secondary structural changes of proteins in fingernails of chronic fatigue syndrome patients from Fourier-transform infrared spectra

2009 Clinica Chimica Acta 402 (01-Feb); 75 – 78

<http://www.scopus.com/inward/record.url?eid=2-s2.0-60649113829&partnerID=40>

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Background: Generally, nails can be an index of health, with abnormalities sometimes found under diseased conditions. Fatigue is also supposed to affect the condition of nails. Possible differences in infrared (IR) spectra of nail plates of chronic fatigue syndrome (CFS) patients compared to healthy control subjects were investigated in this study. Methods: Using an attenuated total reflection (ATR)-Fourier-transform infrared (FTIR) spectrophotometer, spectra in the region of 4000-600 cm^{-1} were obtained. The amide I region was then separated by Fourier deconvolution and curve fitting based on the Gauss and Lorentz formula and revealed differences in the secondary structural content of proteins compared to healthy donors. Results: The specific secondary structural pattern commonly observed in nails of male and female CFS patients in the absence and presence of medication indicated a decreased α -helix content and increased β -sheet content, suggesting reduced levels of normal elements of the nail plate. Conclusions: This provides the first evidence of alterations in the fingernails of CFS patients which could be detected by IR spectroscopy. Possible explanations for the alterations will be discussed. © 2008 Elsevier B.V. All rights reserved.

Ulvestad E.

Chronic fatigue syndrome defies the mind-body-schism of medicine

2008 Medicine, Healthcare and Philosophy 11 (3); 285 – 292

<http://www.scopus.com/inward/record.url?eid=2-s2.0-50249176406&partnerID=40>

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The article maintains that chronic fatigue syndrome can be properly understood only by taking an integrated perspective in which evolutionary, developmental and ecological aspects are considered. The integrative approach, supplemented by a complexity theory and psychoneuroimmunological research, is capable of explaining why there are so few structural aberrations to be found in chronic fatigue syndrome and why specific treatment is so difficult to establish. A major outcome of the investigation, that all individuals with chronic fatigue syndrome are diseased in their own way, emphasises the need to study the development of personalised life histories. It also highlights an ethical dimension; personalised disease defies essentialist thinking on patient management. Another major outcome, which follows from the developmental systems perspective, is the dissolution of ontological mind-body dualism. This in turn allows for a methodological complementation of the biological and phenomenological approaches to knowledge. New research strategies that may help to resolve chronic fatigue syndrome, grounded in the revised perspective on individual development, are suggested. © Springer Science+Business Media B.V. 2008.

Fisher M.McD., Rose M.

Anaesthesia for patients with idiopathic environmental intolerance and chronic fatigue syndrome

2008 British Journal of Anaesthesia 101 (4); 486 – 491

<http://www.scopus.com/inward/record.url?eid=2-s2.0-51849150019&partnerID=40>

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Background. Idiopathic environmental intolerance syndrome (IEI), formerly known as multiple chemical sensitivity syndrome (MCSS), and chronic fatigue syndrome (CFS) are controversial diseases and there is little information in the literature regarding the appropriate conduct of anaesthesia in such patients. Methods. We studied 27 patients referred to our anaesthetic allergy clinic with IEI and CFS and performed literature and web searches on anaesthesia in these disorders. Results. The patients had a significant incidence of adverse events related to anaesthesia which were not allergic in nature. The adverse effects usually occurred postoperatively and were self limiting. Patients with IEI and CFS are not at risk of anaphylaxis and there is no scientific evidence that any drug or technique is excessively hazardous. Neither our patients nor the review of the scientific literature supported available web-based recommendations for the anaesthetic management of patients with IEL and CFS. Conclusions. We suggest that the anaesthetist may be best to use the technique they would use if the patient did not have CFS or IEI but avoid drugs to which there is a history of adverse response. Anaesthesia is likely to be associated with adverse effects in these patients but the effects are not likely to be severe. A series of recommendations for the safe and harmonious conduct of anaesthesia in patients with CFS and IEI are provided. © The Board of Management and Trustees of the British Journal of Anaesthesia 2008. All rights reserved.

Ciccolella M., Stevens S.R., Snell C.R., VanNess M.

Legal and scientific considerations of the exercise stress test

2008 Journal of Chronic Fatigue Syndrome 14 (2); 61 – 75

<http://www.scopus.com/inward/record.url?eid=2-s2.0-39049099835&partnerID=40>

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This article examines the legal and scientific bases on which an exercise stress test can provide medically acceptable evidence of disability for the Chronic Fatigue Syndrome (CFS) patient. To qualify for disability benefits, a claimant must establish the existence of a serious medically determinable impairment (MDI) that causes the inability to work. The single stress test has been used to objectively establish whether a claimant can engage in "substantial gainful employment" and is an important determinant of the award or denial of benefits. A review of case law indicates problems associated with a single test protocol that may be remedied by a "test-retest" protocol. The results of a preliminary study employing this approach indicate that the test-retest protocol addresses problems inherent in a single test and therefore provides an assessment of CFS related disability consistent with both medical and legal considerations. Copyright © by The Haworth Press, Inc. All rights reserved.

Friedberg F., Sohl S., Schmeizer B.

Publication trends in chronic fatigue syndrome: Comparisons with fibromyalgia and fatigue: 1995-2004

2007 Journal of Psychosomatic Research 63 (2); 143 – 146

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34447621933&partnerID=40>

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Objective: In order to identify publishing patterns in chronic fatigue syndrome (CFS), we compared the annual number of peer review articles for CFS, fibromyalgia (FM), and non-CFS fatigue over a recent decade (1995-2004). Method: Citations were drawn from Ovid/Medline, PsychInfo, and the

Journal of Chronic Fatigue Syndrome for peer review articles focusing on CFS, FM, and fatigue for each year of the decade ending in 2004. Statistics included chi-square, tests for differences in proportions, and regression-based curve estimation. Results: The frequency of CFS peer review articles did not significantly change from the first half to the second half of the decade (1995-2004). By comparison, the output of both FM and fatigue articles significantly increased ($P < .0001$). A quadratic model (inverted U shape; $P < .02$) best fit the data for CFS annual publication frequency. By comparison, exponential models best fit the data for both FM ($P < .0001$) and fatigue ($P < .0001$) citations. The highest percentage of citations (15-16%) for both CFS and FM fell within the domains of diagnosis, physiopathology, and psychology. For fatigue, almost one third (31.4%) of the citations were focused on etiology, while psychology (11.5%) and physiopathology (10.4%) articles were the next most cited. Based on first-author affiliation, CFS articles were most likely to originate in the United States (37.7%), England (31.4%), and the Netherlands (4.9%). Conclusion: The output of CFS peer review articles has not increased over the past decade, while the number of FM and fatigue articles has increased substantially. © 2007 Elsevier Inc. All rights reserved.

Carpenter J., Hutchings A., Raine R., Sanderson C.

An experimental study of the influence of individual participant characteristics on formal consensus development

2007 International Journal of Technology Assessment in Health Care 23 (1); 108 – 115

<http://www.scopus.com/inward/record.url?eid=2-s2.0-34247493383&partnerID=40>

Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT, United Kingdom; Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom; Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, United Kingdom

Objectives: The aim of this study was to examine the influence of participants' characteristics on the results produced by formal consensus methods. Methods: The approach was an experimental study of 346 participants in 20 groups rating the appropriateness of four mental health interventions for the treatment of chronic fatigue syndrome, irritable bowel syndrome, and chronic back pain. There were four factors in the design: systematic literature review provided or not, decisions made under realistic or "ideal" resource assumptions, clinically mixed (general practitioners and mental health professionals) or homogenous group (general practitioners only), convened or mail-only group. A group's rating was defined as the median of participants' ratings. The influence of participants' characteristics (age, sex, and specialty) was examined using multilevel models. Results: The largest differences were between the GPs and mental health professionals, both in their initial ratings of the different interventions, and in how much they altered their ratings between rounds. There were smaller but statistically significant ($p < .05$) differences between specialty and age groups in initial ratings for the treatment (by whatever means) of different conditions, and for certain conditions women increased their ratings more than men. Women rated intervention more favorably when assuming "ideal" rather than realistic levels of resources, but men did not. Conclusions: Our findings support the practice of treating professional specialty as an important determinant of the results in consensus panels. Copyright © 2007 Cambridge University Press.

Jason L., Corradi K., Gress S., Williams S., Torres-Harding S.

Causes of death among patients with chronic fatigue syndrome

2006 Health Care for Women International 27 (7); 615 – 626

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33746262972&partnerID=40>

DePaul University, Chicago, IL, United States; Center for Community Research, DePaul University, 990 W. Fullerton Ave., Chicago, IL 60614, United States Chronic fatigue syndrome (CFS) is a debilitating illness affecting thousands of individuals. At the present time, there are few studies that have investigated causes of death for those with this syndrome. The authors analyzed a memorial list

tabulated by the National CFIDS Foundation of 166 deceased individuals who had had CFS. There were approximately three times more women than men on the list. The three most prevalent causes of death were heart failure, suicide, and cancer, which accounted for 59.6% of all deaths. The mean age of those who died from cancer and suicide was 47.8 and 39.3 years, respectively, which is considerably younger than those who died from cancer and suicide in the general population. The implications of these findings are discussed. Copyright © Taylor & Francis Group, LLC.

Browne T., Chalder T.
Chronic fatigue syndrome

2006 Psychiatry 5 (2); 48 - 51

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33845351621&partnerID=40>

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Chronic fatigue syndrome (CFS) is characterized by disabling fatigue that significantly interferes with people's ability to carry out their normal daily activities. This article describes the core symptoms and details diagnostic criteria, in addition to discussing aetiology, risk factors, onset, prognosis and prevalence. Many patients diagnosed with CFS also meet the criteria for common psychiatric disorders, particularly depression. Issues regarding co-morbidity and the relationship between CFS and psychiatric illness are discussed. We outline two popular approaches to understanding CFS; the cognitive behavioural and deconditioning paradigms. The cognitive behavioural model attempts to explain how life stresses can precipitate CFS in predisposed persons, and how cognitive, physiological, behavioural and social factors then interact to perpetuate the illness creating a vicious cycle of chronic fatigue and disability. Deconditioning, a physiological process leading to a decrease in the body's efficiency, reduces the body's capacity for physical exertion, leading to an increase in fatigue symptoms at lower levels of exercise than previously. Treatments for CFS are discussed, with the focus being on two non-pharmacological interventions; cognitive behavioural therapy (CBT) and graded exercise therapy (GET), which have been shown to be very effective in treating CFS. Finally, we discuss CFS in children and adolescents which in recent years, has become more acknowledged. Prevalence and treatment of CFS in children is discussed with special attention being paid to developmental issues. © 2006 Elsevier Ltd. All rights reserved.

Jenkins M., Rayman M.

Nutrient intake is unrelated to nutrient status in patients with chronic fatigue syndrome

2005 Journal of Nutritional and Environmental Medicine 15 (4); 177 – 189

<http://www.scopus.com/inward/record.url?eid=2-s2.0-33745901064&partnerID=40>

Royal London Homeopathic Hospital, Great Ormond Street, London WC1 3HR, United Kingdom; Centre for Nutrition and Food Safety, School of Biomedical and Molecular Sciences, University of Surrey, Guildford GU2 7XH, United Kingdom

Purpose. Previous studies on nutrient intake and status in chronic fatigue syndrome (CFS) were reviewed. Against this background, we investigated whether low mineral and B vitamin status in CFS patients was adequately explained by poor nutritional intake. Subsidiary aims were to explore the demographic, dietary, socio-economic, psychological and general health profiles of CFS patients attending our clinics. Design. A cross-sectional study of 51 CFS patients with biomarker values below the laboratory reference range for minerals and B vitamins. Materials and methods. Dietary and supplemented nutritional intakes were assessed for comparison with laboratory biomarkers in a hospital outpatient clinic. Results. Intakes below the UK reference nutrient intake, particularly of Ca and/or vitamin D, I and Se, were common among these patients. There was little correlation between intakes and biomarkers. Conclusions. Abnormal biomarkers may reflect underlying pathological processes rather than inadequate nutritional intakes and, taken alone, are a poor guide to rational

nutritional supplementation. Nevertheless, there appears to be a case for dietary assessment and modest, targeted, vitamin and mineral supplementation in many of these patients. © 2005 Taylor & Francis.

Whitehead L.

Enhancing the quality of hermeneutic research: Decision trail

2004 Journal of Advanced Nursing 45 (5); 512 – 518

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1642365821&partnerID=40>

Department of Nursing and Midwifery, University of Stirling, Stirling, United Kingdom; Western Isles Campus, University of Stirling, Western Isles Hospital, Macaulay Road, Stornoway, Isle of Lewis HS1 2AF, United Kingdom Background.

Researchers have ethical and professional obligations to produce research of a high standard. The constituents of quality in research appear to differ between authors, leaving readers unsure about which pathway to follow. This can reflect inadequate consideration of the theoretical framework guiding the study. Many papers fail to consider the theoretical underpinnings of the methodology chosen and the link between these and the methods employed. These need to be accessible to readers in order to assess the trustworthiness of the research. Aim. This paper discusses the development of trustworthiness in hermeneutic phenomenological research. Discussion. Referring to a study on lived experience of Chronic Fatigue Syndrome/myalgic encephalitis, I describe the decision trail and discuss the strengths and limitations of the choices made throughout the study. Conclusion. The methodology focused my approach more fully on the importance of recognizing the influences that I brought to the study and the impact of these in generating the data. It highlighted the fact that the process of setting out my horizon can never be complete, the importance of analysing the data at a macro and micro level, acknowledging the evolution of the data over time, and ensuring that analysis does not move beyond the data and out of the hermeneutic circle. In seeking to make the decision trail clear to others, researchers must distill the philosophical principles of the methodology and set these out in a way that is accessible and open to scrutiny.

Schacterle R.S., Komaroff A.L.

A Comparison of Pregnancies That Occur before and after the Onset of Chronic Fatigue Syndrome

2004 Archives of Internal Medicine 164 (4); 401 – 404

<http://www.scopus.com/inward/record.url?eid=2-s2.0-1242275196&partnerID=40>

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Background: Many women with chronic fatigue syndrome (CFS) fear that pregnancy will worsen their condition, increase the risks of maternal complications of pregnancy, or threaten the health of their offspring. Little empirical evidence, however, has been published on this matter. Methods: A detailed questionnaire was administered to 86 women regarding 252 pregnancies that occurred before or after the onset of CFS and the outcomes of these pregnancies were observed. Results: During pregnancy, there was no change in CFS symptoms in 29 (41%), an improvement of symptoms in 21 (30%), and a worsening of symptoms in 20 (29%) of 70 subjects. After pregnancy, there was no change in CFS symptoms in 21 (30%), an improvement of symptoms in 14 (20%), and a worsening of symptoms in 35 (20%) of the subjects. The rates of many complications were similar in pregnancies occurring before the onset and in those occurring after the onset of CFS. There was a higher frequency of spontaneous abortions in the pregnancies occurring after, vs before, the onset of CFS (22 [30%] of 73 pregnancies after vs 13 [8%] of 171 before; $P < .001$), but no differences in the rates of other complications. Developmental delays or learning disabilities were reported more often in the offspring of women who became pregnant after, vs before, the onset of CFS (9 [21%] of 43 children vs 11 [8%] of 139 children; $P = .01$). Conclusions: Pregnancy did not consistently worsen the symptoms of CFS. Most maternal and infant outcomes were not systematically worse in pregnancies occurring after

the onset of CFS. The higher rates of spontaneous abortions and of developmental delays in offspring that we observed could be explained by maternal age or parity differences, and should be investigated by larger, prospective studies with control populations.