

Chronic Fatigue Syndrome

ABSTRACTS

- Avraham Y., 2001. Tyrosine improves appetite, cognition, and exercise tolerance in activity anorexia.
- Bahrke MS., 2000. Evaluation of the ergogenic properties of ginseng: an update.
- Baschetti, R., 1995a. Chronic fatigue syndrome and liquorice.
- Baschetti R., 1995b. Liquorice and chronic fatigue syndrome.
- Baschetti R., 1999. Overlap of chronic fatigue syndrome with primary adrenocortical insufficiency.
- Baschetti R., 2000. Chronic fatigue syndrome: a form of Addison's disease.
- Beckman JS., 1993. Pathological implications of nitric oxide, superoxide and peroxynitrite formation.
- Behan PO., 1990. Effect of high doses of essential fatty acids on the postviral fatigue syndrome.
- Bounous G., 1999. Competition for glutathione precursors between the immune system and the skeletal muscle: pathogenesis of chronic fatigue syndrome.
- Bugard P., 1984. Stabilium 200: Trial Protocol. Clinical Results of the Effects of Stabilium 200 on 40 Asthenic Patients
- Butterworth Jr. C.E., 1993. Folate status, women's health, pregnancy outcome, and cancer.
- CDC., 2001. Chronic Fatigue Syndrome 2001.
- Cleare AJ., 1995. Contrasting neuroendocrine responses in depression and chronic fatigue syndrome.
- Cox IM., 1991. Red blood cell magnesium and chronic fatigue syndrome.
- Crocq L., 1978. Fatigue Study Group inquiry into asthenia in general practice.
- Cullen MR., 1987. The worker with multiple chemical sensitivities: an overview.
- Cullen MR., 1987b. Multiple chemical sensitivities: summary and directions for future investigators.
- De Becker P., 1999. Dehydroepiandrosterone (DHEA) response to i.v. ACTH in patients with chronic fatigue syndrome.
- Deijen JB., 1999. Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course.
- Dimai HP., 1998. Daily oral magnesium supplementation suppresses bone turnover in young adult males.
- Dorman T., 1995. The effectiveness of Garum armoricum (Stabilium) on reducing anxiety in college students.
- Droge W., 1997. Role of cysteine and glutathione in HIV infection and other diseases associated with muscle wasting and immunological dysfunction.
- Elbaz M., 1988. Astheno-depression.
- Fauci AC., 1998. Eds. Harrison's Textbook of Internal Medicine, Fourteenth Edition.
- Forsyth LM., 1999. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome.
- Fulle S., 2000. Specific oxidative alterations in vastus lateralis muscle of patients with the diagnosis of chronic fatigue syndrome.
- Gabe J., 1991. Tranquillisers and health care in crisis.
- Gray JB., 1994. Eicosanoids and essential fatty acid modulation in chronic disease and the chronic fatigue syndrome.
- Haruyama S., Garum extract and improved learning (undated report).
- Hinds G., 1994. Normal red cell magnesium concentrations and magnesium loading tests in patients with chronic fatigue syndrome.
- Horrobin DF., 1990. Post-viral fatigue syndrome, viral infections in atopic eczema, and essential fatty acids.
- Jacobson W., 1993. Serum folate and chronic fatigue syndrome.
- Jeffcoate WJ., 1999. Chronic fatigue syndrome and functional hypoadrenia? fighting vainly the old ennui.
- Jefferies WM., 1994. Mild adrenocortical deficiency, chronic allergies, autoimmune disorders and the chronic fatigue syndrome: a continuation of the cortisone story.
- Judy W., 1996. Presentation to the 37th Annual Meeting of the American College of Nutrition, Southeastern Institute of Biomedical Research.
- Kelly GS., 1998. L-Carnitine: therapeutic applications of a conditionally-essential amino acid.
- Kingsbury KJ., 1998. Contrasting plasma free amino acid patterns in elite athletes: association with fatigue and infection.

- Kodama M., 1996. The value of the dehydroepiandrosterone-annexed vitamin C infusion treatment in the clinical control of chronic fatigue syndrome (CFS). II. Characterization of CFS patients with special reference to their response to a new vitamin C infusion treatment.
- Komaroff AL., 1998. Chronic fatigue syndrome: an update.
- Kuratsune H., 1998. Dehydroepiandrosterone sulfate deficiency in chronic fatigue syndrome.
- Le Poncin M., 2000. Stabium and chronic fatigue. The positive role of a nutraceutical in memory and cognitive function and symptoms of chronic fatigue in adults.
- Logan AC., 2001. Chronic fatigue syndrome: oxidative stress and dietary modifications.
- Manian FA., 1994. Simultaneous measurement of antibodies to Epstein-Barr virus, human herpesvirus 6, herpes simplex virus types 1 and 2, and 14 enteroviruses in chronic fatigue syndrome: is there evidence of activation of a nonspecific polyclonal immune response?
- Manuel y Keenoy B., 2000. Magnesium status and parameters of the oxidant-antioxidant balance in patients with chronic fatigue: effects of supplementation with magnesium.
- Manuel y Keenoy B., 2001. Antioxidant status and lipoprotein peroxidation in chronic fatigue syndrome.
- McCully KK., 1996. Reduced oxidative muscle metabolism in chronic fatigue syndrome.
- McCully KK., 1999. Impaired oxygen delivery to muscle in chronic fatigue syndrome.
- Neeck G., 2000. Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome.
- Ojo-Amaize EA., 1994. Decreased natural killer cell activity is associated with severity of chronic fatigue immune dysfunction syndrome.
- Owasoyo JO., 1992. Tyrosine and its potential use as a countermeasure to performance decrement in military sustained operations.
- Pall ML., 2000. Elevated, sustained peroxynitrite levels as the cause of chronic fatigue syndrome.
- Pall ML., 2001. Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite.
- Parker AJ., 2001. The neuroendocrinology of chronic fatigue syndrome and fibromyalgia.
- Plioplys AV., 1995. Serum levels of carnitine in chronic fatigue syndrome: clinical correlates.
- Plioplys AV., 1997. Amantadine and L-carnitine treatment of Chronic Fatigue Syndrome.
- Powers SK., 1999. Exercise training-induced alterations in skeletal muscle antioxidant capacity: a brief review.
- Radi R., 1994. Inhibition of mitochondrial electron transport by peroxynitrite.
- Regland B., 1997. Increased concentrations of homocysteine in the cerebrospinal fluid in patients with fibromyalgia and chronic fatigue syndrome.
- Reid S., 2000. Chronic fatigue syndrome.
- Richards RS., 2000. Blood parameters indicative of oxidative stress are associated with symptom expression in chronic fatigue syndrome.
- Scott LV., 1999. Differences in adrenal steroid profile in chronic fatigue syndrome, in depression and in health.
- Stejskal VD., 1999. Metal-specific lymphocytes: biomarkers of sensitivity in man.
- Sussman N., 1993. How to manage anxious patients who are depressed.
- Sussman N., 1993. Treating anxiety while minimizing abuse and dependence.
- Torpy DJ., 1996. The three-way interactions between the hypothalamic-pituitary-adrenal and gonadal axes and the immune system.
- Verillo EF., 1997. Chronic Fatigue Syndrome.
- Warren G., 1999. The role of essential fatty acids in chronic fatigue syndrome. A case-controlled study of red-cell membrane essential fatty acids (EFA) and a placebo-controlled treatment study with high dose of EFA.
- Werbach MR., 2000. Nutritional strategies for treating chronic fatigue syndrome.
- Tyrosine improves appetite, cognition, and exercise tolerance in activity anorexia.**

Avraham Y, Hao S, Mendelson S, Berry EM. Department of Human Nutrition and Metabolism, Hebrew University-Hadassah Medical School, Jerusalem, Israel 91120.

Med Sci Sports Exerc 2001 Dec;33(12):2104-10

PURPOSE: We have modified for mice the activity wheel model of Routtenberg to study the effects of tyrosine on exercise tolerance, behavior, and brain neurochemistry. **METHODS:** Mice were fed for 2 h.d(-1) over a 2-wk period. During the second week, each group was injected daily with either saline or tyrosine (100 mg.kg(-1).d(-1)) and exercised on a running wheel. Controls were in cages with inactivated wheels and received the same treatment and feeding protocols as the experimental groups. Food consumption and cognitive function (eight-arm maze) were evaluated for 1 wk. Brains were then assayed for adrenergic and serotonergic metabolites. **RESULTS:** Activity together with a restricted diet caused extreme weight loss (27%) (< 0.001) together with decreased food consumption (22%) (< 0.001). Tyrosine restored food consumption to that of the controls (< 0.001) with no

effect on weight, since there was a 22% increase in activity (< 0.001). Saline injections caused an 18% decrease in activity (< 0.001). Both activity and tyrosine improved maze performance (< 0.05). In the hypothalamus, activity caused a significant increase in 5-hydroxytryptamine (5-HT) (< 0.001), 5-hydroxyindoleacetic acid (5-HIAA) (< 0.01), and dopamine (< 0.05); tyrosine prevented the increase in 5-HT (< 0.05) and increased 5-HIAA in the controls (< 0.01). With regard to hippocampal 5-HT, there was a significant increase in 5-HIAA following activity (< 0.05), whereas tyrosine caused significant increase in 5-HIAA in the controls (< 0.01). Activity significantly decreased the level of hippocampal 3,4-dihydroxyphenylacetic acid (DOPAC), whereas tyrosine decreased its level only in the controls (both at < 0.0001). The level of tyrosine hydroxylase increased with activity (< 0.05), and tyrosine decreased it significantly (< 0.05). **CONCLUSION:** Activity anorexia is associated with increased hypothalamic 5-HT concentrations. Tyrosine administration reverses this, and significantly improves food consumption, cognitive behavior, and activity performance. Such nutritional modulations may have implications for the treatment of eating disorders and, in normal circumstances, tyrosine may improve exercise tolerance and delay fatigue.

Evaluation of the ergogenic properties of ginseng: an update.

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Sports Med 2000 Feb;29(2):113-33

Ginseng has been used in the Orient for several thousand years as an 'adaptogenic' as well as a 'restorative' agent. It has been used to treat nervous disorders, anaemia, wakefulness, dyspnoea, forgetfulness and confusion, prolonged thirst, decreased libido, chronic fatigue, angina and nausea. Although the mechanisms underlying the alleged effects of ginseng remain to be elucidated, there is an extensive animal literature dealing with the effects of ginseng on the cardiovascular system, central nervous system, endocrine system, metabolism, and immune system. In our previous review dealing with the efficacy of ginseng, we concluded that while studies with animals show that ginseng, or its active components, may prolong survival to physical or chemical stress, there is generally a lack of controlled research demonstrating the ability of ginseng to improve or prolong performance in fatigued humans. In this review, we extend our earlier analysis on the potential efficacy of ginseng use in the enhancement of physical performance and modification of fatigue states. Our analysis reveals that published literature appearing since our earlier review has not resolved the equivocal nature of research evidence involving animals or humans. Also, the lack of unanimity in this research can be explained on the basis of various methodological problems such as inadequate sample size and lack of double-blind, control and placebo paradigms. In addition, the absence of acceptable approaches to the problem of 'sourcing', in concert with an absence of compliance data in human research, further complicates the interpretation of this research literature. Nevertheless, the use of ginseng continues to grow, and current sales are estimated to be over \$US300 million annually. There is clearly a need for systematic research dealing with the efficacy of ginseng, and this research needs to take into account basic, fundamental design considerations if there is to be any hope of establishing whether or not ginseng possesses efficacy.

Chronic fatigue syndrome and liquorice.

Baschetti, R.

N.Z. Med. J. 1995a; 108(998): 156-7.

No abstract available

Liquorice and chronic fatigue syndrome.

Baschetti, R.

N.Z. Med. J. 1995b; 108(1002): 259.

No abstract available

Overlap of chronic fatigue syndrome with primary adrenocortical insufficiency.

Baschetti, R.

Horm. Metab. Res. 1999; 31(7): 439.

No abstract available

Chronic fatigue syndrome: a form of Addison's disease.

Baschetti, R.

J. Intern. Med. 2000; 247(6): 737-9.

No abstract available

Pathological implications of nitric oxide, superoxide and peroxynitrite formation.

Beckman, J.S., Crow, J.P.

Biochem. Soc. Trans. 1993 May; 21(2): 330-4.

No abstract available

Effect of high doses of essential fatty acids on the postviral fatigue syndrome.

Behan PO, Behan WM, Horrobin D. Department of Neurology, University of Glasgow, Scotland.

Acta Neurol Scand 1990 Sep;82(3):209-16

Sixty-three adults with the diagnosis of the postviral fatigue syndrome were enrolled in a double-blind, placebo-controlled study of essential fatty acid therapy. The patients had been ill for from one to three years after an apparently viral infection, suffering from severe fatigue, myalgia and a variety of psychiatric symptoms. The preparation given contained linoleic, gamma-linolenic, eicosapentaenoic and docosahexaenoic acids and either it, or the placebo, was given as 8 x 500 mg capsules per day over a 3-month period. The trial was parallel in design and patients were evaluated at entry, one month and three months. In consultation with the patient the doctors assessed overall condition, fatigue, myalgia, dizziness, poor concentration and depression on a 3-point scale. The essential fatty acid composition of their red cell membrane phospholipids was analysed at the first and last visits. At 1 month, 74% of patients on active treatment and 23% of those on placebo assessed themselves as improved over the baseline, with the improvement being much greater in the former. At 3 months the corresponding figures were 85% and 17% (p less than 0.0001) since the placebo group had reverted towards the baseline state while those in the active group showed continued improvement. The essential fatty acid levels were abnormal at the baseline and corrected by active treatment. There were no adverse events. We conclude that essential fatty acids provide a rational, safe and effective treatment for patients with the post-viral fatigue syndrome.

Competition for glutathione precursors between the immune system and the skeletal muscle: pathogenesis of chronic fatigue syndrome.

Bounous G, Molson J. Department of Surgery, McGill University, and Medical Research Council of Canada.

Med Hypotheses 1999 Oct;53(4):347-9

The chronic fatigue syndrome (CFS) is typically associated or follows a recognized or presumed infection. Abnormalities of both humoral and cellular immunity have been demonstrated in a substantial proportion of patients with CFS. The most consistent findings are of impaired lymphocyte responses to mitogen. As an antioxidant, glutathione (GSH) is essential for allowing the lymphocyte to express its full potential without being hampered by oxiradical accumulation. Hence, protracted challenge of the immunocytes may lead to cellular GSH depletion. Because GSH is also essential to aerobic muscular contraction, an undesirable competition for GSH precursors between the immune and muscular systems may develop. It is conceivable that the priority of the immune system for the survival of the host has drawn to this vital area the ever-diminishing GSH precursors, thus depriving the skeletal muscle of adequate GSH precursors to sustain a normal aerobic metabolism resulting in fatigue and eventually myalgia.

Stabilium 200: Trial Protocol. Clinical Results of the Effects of Stabilium 200 on 40 Asthenic Patients

Bugard, P.

1984 May 4. Paris: Saint-Anne Hospital Group/Fatigue Study Group.

No abstract available.

Folate status, women's health, pregnancy outcome, and cancer

Butterworth Jr. C.E. Dept. of Nutrition Sciences, University of Alabama, Birmingham, AL 35294 United States

Key observations by Dr. Lucy Wills 65 years ago have led to the identification of folate as a nutrient essential for the prevention of megaloblastic anemia of pregnancy. The more recently discovered relationships of folate status to cervical dysplasia, neural tube defects, and atherosclerosis are reviewed here.

Chronic Fatigue Syndrome 2001

CDC

2001 Sep 13. Atlanta, GA: Centers for Disease

Control/National Center for Infectious Diseases (www.cdc.gov/ncidod/diseases/cfs/).

Contrasting neuroendocrine responses in depression and chronic fatigue syndrome.

Cleare AJ, Bearn J, Allain T, McGregor A, Wessely S, Murray RM, O'Keane V. Maudsley Hospital, Denmark Hill, London, UK.

J Affect Disord 1995 Aug 18;34(4):283-9

Hypothalamic-pituitary-adrenal (HPA) axis and central 5-HT function were compared in chronic fatigue syndrome (CFS), depression and healthy states. 10 patients with CFS and 15 patients with major depression were matched for age, weight, sex and menstrual cycle with 25 healthy controls. Baseline-circulating cortisol levels were highest in the depressed, lowest in the CFS and intermediate between the two in the control group ($P = 0.01$). Prolactin responses to the selective 5-HT-releasing agent d-fenfluramine were lowest in the depressed, highest in the CFS and intermediate between both in the healthy group ($P = 0.01$). Matched pair analysis confirmed higher prolactin responses in CFS patients than controls ($P = 0.05$) and lower responses in depressed patients than controls ($P = 0.003$). There were strong inverse correlations between prolactin and cortisol responses and baseline cortisol values. These data confirm that depression is associated with hypercortisolaemia and reduced central 5-HT neurotransmission and suggest that CFS may be associated with hypocortisolaemia and increased 5-HT function. The opposing responses in CFS and depression may be related to reversed patterns of behavioural dysfunction seen in these conditions. These findings attest to biological distinctions between these disorders.

Red blood cell magnesium and chronic fatigue syndrome.

Cox IM, Campbell MJ, Dowson D. Medical School, University of Southampton, UK.

Lancet 1991 Mar 30;337(8744):757-60

The hypotheses that patients with chronic fatigue syndrome (CFS) have low red blood cell magnesium and that magnesium treatment would improve the wellbeing of such patients were tested in a case-control study and a randomised, double-blind, placebo-controlled trial, respectively. In the case-control study, 20 patients with CFS had lower red cell magnesium concentrations than did 20 healthy control subjects matched for age, sex, and social class (difference 0.1 mmol/l, 95% confidence interval [CI] 0.05 to 0.15). In the clinical trial, 32 patients with CFS were randomly allocated either to intramuscular magnesium sulphate every week for 6 weeks (15 patients) or to placebo (17). Patients treated with magnesium claimed to have improved energy levels, better emotional state, and less pain, as judged by changes in the Nottingham health profile. 12 of the 15 treated patients said that they had benefited from treatment, and in 7 patients energy score improved from the maximum to the minimum. By contrast, 3 of the 17 patients on placebo said that they felt better (difference 62%, 95% CI 35 to 90), and 1 patient had a better energy score. Red cell magnesium returned to normal in all patients on magnesium but in only 1 patient on placebo. The findings show that magnesium may have a role in CFS.

Fatigue Study Group inquiry into asthenia in general practice.

Crocq, L., Bugard, P., Viaud, P.

Psychol. Med. 1978; 10: 1943-53.

No abstract available.

The worker with multiple chemical sensitivities: an overview.

Cullen, M.R.

Occup. Med. 1987a Oct-Dec; 2(4): 655-61.

No abstract available.

Multiple chemical sensitivities: summary and directions for future investigators.

Cullen, M.R.

Occup. Med. 1987b Oct-Dec; 2(4): 801-4.

No abstract available.

Dehydroepiandrosterone (DHEA) response to i.v. ACTH in patients with chronic fatigue syndrome.

De Becker P, De Meirleir K, Joos E, Campine I, Van Steenberge E, Smits J, Velkeniers B. Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Belgium. pdbeck@minf.vub.ac.be

Horm Metab Res 1999 Jan;31(1):18-21

Previous studies have demonstrated concentrating neuroendocrinological disturbances in chronic fatigue syndrome (CFS) patients, concentrating in particular on low cortisol levels and a hypothalamic deficiency. In order to investigate the dynamic response of the adrenal glands, we measured dehydroepiandrosterone (DHEA) in serum after adreno-corticotrophic hormone (ACTH) stimulation during 60 minutes in 22 CFS-patients and 14 healthy controls. We found normal basal DHEA levels, but a blunted serum DHEA response curve to i.v. ACTH injection. This observation adds to the large amount of evidence of endocrinological abnormalities in CFS. Relative glucocorticoid deficiency might contribute to the overall clinical picture in CFS, and could explain some of the immunological disturbances observed in this syndrome.

Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course.

Deijen JB, Wientjes CJ, Vullings HF, Cloin PA, Langefeld JJ. Department of Clinical Neuropsychology, Vrije Universiteit, Amsterdam, The Netherlands. jb.deijen@psy.vu.nl

Brain Res Bull 1999 Jan 15;48(2):203-9

The effects of the amino acid tyrosine on cognitive task performance were studied on a group of 21 cadets during a demanding military combat training course. In addition, the effects on mood, blood pressure and the norepinephrine metabolite MHPG were determined. Ten subjects received five daily doses of a protein-rich drink containing 2 g tyrosine, and 11 subjects received a carbohydrate rich drink with the same amount of calories (255 kcal). Assessments were made both immediately prior to the combat course and on the 6th day of the course. The group supplied with the tyrosine-rich drink performed better on a memory and a tracking task than the group supplied with the carbohydrate-rich drink. In addition, the supplementation of tyrosine decreased systolic blood pressure. No effects on mood were found. These findings suggest that supplementation with tyrosine may, under operational circumstances characterized by psychosocial and physical stress, reduce the effects of stress and fatigue on cognitive task performance.

Daily oral magnesium supplementation suppresses bone turnover in young adult males.

Dimai HP, Porta S, Wirnsberger G, Lindschinger M, Pamperl I, Dobnig H, Wilders-Truschnig M, Lau KH. Department of Endocrinology, University of Graz Medical School, Austria.

J Clin Endocrinol Metab 1998 Aug;83(8):2742-8

This study examined the effects of daily oral magnesium (Mg) supplementation on bone turnover in 12 young (27-36 yr old) healthy men. Twelve healthy men of matching age, height, and weight were recruited as the control group. The study group received orally 15 mmol Mg (Magnosolv powder, Asta Medica) daily in the early afternoon with 2-h fasting before and after Mg intake. Fasting blood and second void urine samples were collected in the early morning on days 0, 1, 5, 10, 20, and 30, respectively. Total and ionized Mg²⁺ and calcium (Ca²⁺), and intact PTH (iPTH) levels were determined in blood samples. Serum biochemical markers of bone formation (i.e. C-terminus of type I procollagen peptide and osteocalcin) and resorption (i.e. type I collagen telopeptide) and urinary

Mg level adjusted for creatinine were measured. In these young males, 30 consecutive days of oral Mg supplementation had no significant effect on total circulating Mg level, but caused a significant reduction in the serum ionized Mg²⁺ level after 5 days of intake. The Mg supplementation also significantly reduced the serum iPTH level, which did not appear to be related to changes in serum Ca²⁺ because the Mg intake had no significant effect on serum levels of either total or ionized Ca²⁺. There was a strong positive correlation between serum iPTH and ionized Mg²⁺ ($r = 0.699$; < 0.001), supporting the contention that decreased serum iPTH may be associated with the reduction in serum ionized Mg²⁺. Mg supplementation also reduced levels of both serum bone formation and resorption biochemical markers after 1-5 days, consistent with the premise that Mg supplementation may have a suppressive effect on bone turnover rate. Covariance analyses revealed that serum bone formation markers correlated negatively with ionized Mg²⁺ ($r = -0.274$ for type I procollagen peptide and -0.315 for osteocalcin), but not with iPTH or ionized Ca²⁺. Thus, the suppressive effect on bone formation may be mediated by the reduction in serum ionized Mg²⁺ level (and not iPTH or ionized Ca²⁺). In summary, this study has demonstrated for the first time that oral Mg supplementation in normal young adults caused reductions in serum levels of iPTH, ionized Mg²⁺, and biochemical markers of bone turnover. In conclusion, oral Mg supplementation may suppress bone turnover in young adults. Because increased bone turnover has been implicated as a significant etiological factor for bone loss, these findings raise the interesting possibility that oral Mg supplementation may have beneficial effects in reducing bone loss associated with high bone turnover, such as age-related osteoporosis.

The effectiveness of Garom armoricum (Stabilium) on reducing anxiety in college students.

Dorman, T., Bemard, L., Glaze, P., Hogan, J., Skinner, R., Nelson, D., Bowker, L., Head, D.

J. Adv. Med. 1995 Fall; 8(3): 193-200.

No abstract available.

Role of cysteine and glutathione in HIV infection and other diseases associated with muscle wasting and immunological dysfunction.

Droge W, Holm E. Division of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

FASEB J 1997 Nov;11(13):1077-89

The combination of abnormally low plasma cystine and glutamine levels, low natural killer (NK) cell activity, skeletal muscle wasting or muscle fatigue, and increased rates of urea production defines a complex of abnormalities that is tentatively called "low CG syndrome." These symptoms are found in patients with HIV infection, cancer, major injuries, sepsis, Crohn's disease, ulcerative colitis, chronic fatigue syndrome, and to some extent in overtrained athletes. The coincidence of these symptoms in diseases of different etiological origin suggests a causal relationship. The low NK cell activity in most cases is not life-threatening, but may be disastrous in HIV infection because it may compromise the initially stable balance between the immune system and virus, and trigger disease progression. This hypothesis is supported by the coincidence observed between the decrease of CD4⁺ T cells and a decrease in the plasma cystine level. In addition, recent studies revealed important clues about the role of cysteine and glutathione in the development of skeletal muscle wasting. Evidence suggests that 1) the cystine level is regulated primarily by the normal postabsorptive skeletal muscle protein catabolism, 2) the cystine level itself is a physiological regulator of nitrogen balance and body cell mass, 3) the cyst(e)ine-mediated regulatory circuit is compromised in various catabolic conditions, including old age, and 4) cysteine supplementation may be a useful therapy if combined with disease-specific treatments such as antiviral therapy in HIV infection.

Astheno-depression.

Elbaz, M.

Cah. Biother. 1988 Dec.

No abstract available.

Eds. Harrison's Textbook of Internal Medicine, Fourteenth Edition 1998.

Fauci, A.C., Martin, J.B., Braunwald, E. et al.,

New York: McGraw-Hill.

Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome.

Forsyth LM, Preuss HG, MacDowell AL, Chiazze L Jr, Birkmayer GD, Bellanti JA. Department of Pediatrics, Georgetown University School of Medicine, Washington, D.C., USA.

Ann Allergy Asthma Immunol 1999 Feb;82(2):185-91

BACKGROUND: Chronic fatigue syndrome (CFS) is a disorder of unknown etiology, consisting of prolonged, debilitating fatigue, and a multitude of symptoms including neurocognitive dysfunction, flu-like symptoms, myalgia, weakness, arthralgia, low-grade fever, sore throat, headache, sleep disturbances, and swelling and tenderness of lymph nodes. No effective treatment for CFS is known. **OBJECTIVE:** The purpose of the study was to evaluate the efficacy of the reduced form of nicotinamide adenine dinucleotide (NADH) i.e., ENADA the stabilized oral absorbable form, in a randomized, double-blind, placebo-controlled crossover study in patients with CFS. Nicotinamide adenine dinucleotide is known to trigger energy production through ATP generation which may form the basis of its potential effects. **METHODS:** Twenty-six eligible patients who fulfilled the Center for Disease Control and Prevention criteria for CFS completed the study. Medical history, physical examination, laboratory studies, and questionnaire were obtained at baseline, 4, 8, and 12 weeks. Subjects were randomly assigned to receive either 10 mg of NADH or placebo for a 4-week period. Following a 4-week washout period, subjects were crossed to the alternate regimen for a final 4-week period. **RESULTS:** No severe adverse effects were observed related to the study drug. Within this cohort of 26 patients, 8 of 26 (31%) responded favorably to NADH in contrast to 2 of 26 (8%) to placebo. Based upon these encouraging results we have decided to conduct an open-label study in a larger cohort of patients. **CONCLUSION:** Collectively, the results of this pilot study indicate that NADH may be a valuable adjunctive therapy in the management of the chronic fatigue syndrome and suggest that further clinical trials be performed to establish its efficacy in this clinically perplexing disorder.

Specific oxidative alterations in vastus lateralis muscle of patients with the diagnosis of chronic fatigue syndrome.

Fulle S, Mecocci P, Fano G, Vecchiet I, Vecchini A, Racciotti D, Cherubini A, Pizzigallo E, Vecchiet L, Senin U, Beal MF. Lab. Interuniversitario di Miologia, Dip. Biologia Cellulare e Molecolare, Universita di Perugia, Perugia, Italy.

Free Radic Biol Med 2000 Dec 15;29(12):1252-9

Chronic fatigue syndrome (CFS) is a poorly understood disease characterized by mental and physical fatigue, most often observed in young white females. Muscle pain at rest, exacerbated by exercise, is a common symptom. Although a specific defect in muscle metabolism has not been clearly defined, yet several studies report altered oxidative metabolism. In this study, we detected oxidative damage to DNA and lipids in muscle specimens of CFS patients as compared to age-matched controls, as well as increased activity of the antioxidant enzymes catalase, glutathione peroxidase, and transferase, and increases in total glutathione plasma levels. From these results we hypothesize that in CFS there is oxidative stress in muscle, which results in an increase in antioxidant defenses. Furthermore, in muscle membranes, fluidity and fatty acid composition are significantly different in specimens from CFS patients as compared to controls and to patients suffering from fibromyalgia. These data support an organic origin of CFS, in which muscle suffers oxidative damage.

Tranquillisers and health care in crisis.

Gabe J, Bury M. Department of Community Medicine, University College and Middlesex Hospital School of Medicine, London, U.K.

Soc Sci Med 1991;32(4):449-54

This paper addresses the issue of the crisis of therapeutic efficacy in Britain through a case study of benzodiazepine tranquilliser dependence. The paper traces the rise of tranquillisers and the crisis of legitimacy in prescribing behaviour in the 1980s. It documents growing concern with dependence and the claims made about it by experts and consumer groups. The paper goes on to analyse the importance of the television in these claims-making activity and its influence in shaping perceptions. Finally, we consider the implications of these events for the future of benzodiazepine tranquillisers as a form of treatment.

Eicosanoids and essential fatty acid modulation in chronic disease and the chronic fatigue syndrome.

Gray JB, Martinovic AM.

Med Hypotheses 1994 Jul;43(1):31-42

Abnormalities of Essential Fatty Acid (EFA) incorporation into phospholipid are found in chronic diseases. More recently changes in circulating EFA metabolites (EFAM) together with EFAM hypo-responsiveness of immune cells and EFAM production from cells have been found associated with disease. We hypothesize that changes in ratio of EFAMs are the normal physiological responses to stressors, but when stressors are excessive or prolonged, EFAM systems may become unpredictably hypo-responsive owing to factors such as receptor down regulation and substrate depletion. In time, many homeostatic system become deranged and held in

that state by minor stressors. Literature review of chronic fatigue syndrome (CFS) shows hyper and hypo-responsiveness in immune function, several Hypothalamo-Pituitary (HP) axes and sympathetic nervous system, all relatable to dysfunctional changes in EFA metabolism. For the first time, we explain chronic immune system activation and hypo-responsive immune function in CFS; through EFAMs. Dietary EFA modulation (DEFA) can alter ratios of both membrane EFAs and produced EFAMs, and if maintained can restore hypo-responsive function. We discuss dietary strategies and relevance in CFS, and a case series of CFS patients applying DEFA with other titrated published managements which saw 90% gaining improvement within 3 months and more than 2/3 fit for full time duties. This hypothesis and DEFA may have relevance in other chronic conditions.

Garum extract and improved learning (undated report).

Haruyama, S.

Denetoshi Hospital, Koesi, Japan.

Normal red cell magnesium concentrations and magnesium loading tests in patients with chronic fatigue syndrome.

Hinds G, Bell NP, McMaster D, McCluskey DR. Department of Medicine, Queen's University of Belfast, Northern Ireland, UK.

Ann Clin Biochem 1994 Sep;31 (Pt 5):459-61

Red blood cell magnesium concentrations were measured in samples from 89 patients who fulfilled the diagnostic criteria for chronic fatigue syndrome and the results compared to those found in an age and sex matched group selected from the normal population. No significant difference was found. Six patients were further investigated using a magnesium loading test to determine if there was any evidence of magnesium deficiency associated with this disorder. None was found. There is therefore no indication for the use of magnesium therapy in the management of this condition.

Post-viral fatigue syndrome, viral infections in atopic eczema, and essential fatty acids.

Horrobin DF. Efamol Research Institute, Kentville, Nova Scotia, Canada.

Med Hypotheses 1990 Jul;32(3):211-7

Three clinical observations relating to viral infections are well-known but poorly understood. These are: the susceptibility of people with atopic eczema to viral infections; the occasional precipitation of an atopic syndrome by viral infections; the occurrence of a fatigue syndrome following viral infections. A unifying hypothesis is presented which explains these observations in terms of the interactions between viral infections and essential fatty acid (EFA) metabolism. Key elements of the hypothesis are the facts that interferon requires 6-desaturated EFAs in order to exert its anti-viral effects, that people with atopic eczema have low levels of 6-desaturated EFAs, and that viruses, as part of their attack strategy, may reduce the ability of cells to make 6-desaturated EFAs. The hypothesis has practical implications for the treatment of patients with viral infections.

Serum folate and chronic fatigue syndrome.

Jacobson W, Saich T, Borysiewicz LK, Behan WM, Behan PO, Wreghitt TG. University Department of Paediatrics, Addenbrooke's Hospital, Cambridge, UK.

Neurology 1993 Dec;43(12):2645-7

We assayed serum folate levels of 60 patients with chronic fatigue syndrome (CFS) and found that 50% had values below 3.0 micrograms/l. Some patients with CFS are deficient in folic acid.

Chronic fatigue syndrome and functional hypoadrenia-fighting vainly the old ennui.

Jeffcoate, W.J.

Lancet 1999; 353(9151): 424-5.

No abstract available.

Mild adrenocortical deficiency, chronic allergies, autoimmune disorders and the chronic fatigue syndrome: a continuation of the cortisone story.

Jefferies WM. Case-Western Reserve University School of Medicine, Cleveland, Ohio.

Med Hypotheses 1994 Mar;42(3):183-9

The possibility that patients with disorders that improve with administration of large, pharmacologic dosages of glucocorticoids, such as chronic allergies and autoimmune disorders, might have mild deficiency of cortisol production or utilization has received little attention. Yet evidence that patients with rheumatoid arthritis improved with small, physiologic dosages of cortisol or cortisone acetate was reported over 25 years ago, and that patients with chronic allergic disorders or unexplained chronic fatigue also improved with administration of such small dosages was reported over 15 years ago, suggesting that these disorders might be associated with mild adrenocortical deficiency. The apparent reasons for the failure of these reports to be confirmed or mentioned in medical textbooks and the facts needed to restore perspective are reviewed, and the need for further studies of the possible relationship of a mild deficiency of the production or utilization of cortisol and possibly other normal adrenocortical hormones to the development of these disorders is discussed.

Presentation to the 37th Annual Meeting of the American College of Nutrition, Southeastern Institute of Biomedical Research,

Judy, W.

October 13, 1996, Bradenton, FL.

L-Carnitine: therapeutic applications of a conditionally-essential amino acid.

Kelly GS.

Altern Med Rev 1998 Oct;3(5):345-60

A trimethylated amino acid roughly similar in structure to choline, carnitine is a cofactor required for transformation of free long-chain fatty acids into acylcarnitines, and for their subsequent transport into the mitochondrial matrix, where they undergo beta-oxidation for cellular energy production. Mitochondrial fatty acid oxidation is the primary fuel source in heart and skeletal muscle, pointing to the relative importance of this nutrient for proper function in these tissues. Although L-carnitine deficiency is an infrequent problem in a healthy, well-nourished population consuming adequate protein, many individuals within the population appear to be somewhere along a continuum, characterized by mild deficiency at one extreme, and tissue pathology at the other. Conditions which seem to benefit from exogenous supplementation of L-carnitine include anorexia, chronic fatigue, coronary vascular disease, diphtheria, hypoglycemia, male infertility, muscular myopathies, and Rett syndrome. In addition, preterm infants, dialysis patients, and HIV+ individuals seem to be prone to a deficiency of L-carnitine, and benefit from supplementation. Although available data on L-carnitine as an ergogenic aid is not compelling, under some experimental conditions pretreatment has favored aerobic processes and resulted in improved endurance performance.

Contrasting plasma free amino acid patterns in elite athletes: association with fatigue and infection.

Kingsbury, K.J., Kay, L., Hjelm, M.

Br. J. Sports Med. 1998 Mar; 32(1): 25-32; discussion, 32-3; comment, Br. J. Sports Med. Sep; 32(3): 266-7.

No abstract available.

The value of the dehydroepiandrosterone-annexed vitamin C infusion treatment in the clinical control of chronic fatigue syndrome (CFS). II. Characterization of CFS patients with special reference to their response to a new vitamin C infusion treatment.

Kodama M, Kodama T, Murakami M. Kodama Research Institute of Preventive Medicine, Nagoya, Japan.

In Vivo 1996 Nov-Dec;10(6):585-96

This study is a counterpart of the pilot study on the clinical management of chronic fatigue syndrome (CFS) by the combined use of the old (annex-free) and the new (dehydro-epiandrosterone- annexed) vitamin C infusion treatments with and without oral intake of erythromycin and chloramphenicol. We were motivated to start this clinical study by 2 reasons: i) we have made a success in the clinical management of autoimmune disease and allergy by use of the old megadose vitamin C infusion treatment, and we therefore took up CFS as a good candidate for vitamin C infusion treatment; ii) In 1995, we received a total of 313 chronic pneumonia patients

whose clinical course showed a good fitness to the criteria of CFS. We assessed the nature of the disease by investigating the clinicoepidemiological aspect of our patients on the one hand and the response of the disease to both the old and new vitamin C infusion treatments with and without the use of 2 antibiotics on the other hand. Results are summarized as follows: a) the analysis of the medical records of our outpatients revealed that chronic type pneumonia epidemic in Nagoya Japan, with its onset of January 1995, showed no sign of its extinction by the end of May 1996. The patient population contained no patients under 15 years of age, and showed a distinct female predominance in the patient number (207 females versus 106 males). In 1995, we also experienced a simple cold epidemic with its onset of January 1995 (162 males and 224 females). The majority of simple cold patients were under 25 years of age in both sexes. b) A chronic type pneumonia patient was distinguished from a simple cold patient in 2 respects: firstly the former required prolonged medical care (over 1 month) resulting in an incomplete cure and return to medical care upon the recurrence of disease, whereas the latter required short-term medical care (mostly within 1 week) ending up with complete cure. Secondly, the former required the long term use of 2 antibiotics (erythromycin and chloramphenicol) together with regular practice of the old and new vitamin C infusion treatments for disease control, whereas the latter recovered from the disease after the short time use of a set of conventional cold remedies. c) The clinical manifestations of our chronic pneumonia patients showed good fitness to the criteria of CFS. d) CFS was distinguished from autoimmune disease-allergy complex by the method of clinical control: the former required the long-term use of 2 antibiotics together with regular practice of the old and new vitamin C infusion treatments, whereas the latter was controllable by the single use of the old vitamin C infusion treatment. e) The combined use of the old and new vitamin C infusion treatments rather than the single use of the old vitamin C infusion treatment was more effective for the control of CFS-a finding which suggests that deficient activities of both endogenous glucocorticoid and endogenous androgen in a CFS patient are somehow related to the genesis and further development of CFS. f) Evidence was available to indicate that the sole use of the new vitamin C infusion treatment may induce a state of gonadal steroid excess together with various other problems in the recipient. The maintenance of a good balance between the old vitamin C infusion set (glucocorticoid-inducer) and the new vitamin C infusion set (inducer of both glucocorticoid and gonadal steroids) in their use was of prime importance for the successful control of CFS. g) The historical significance of CFS epidemic in 1995, and in Nagoya-Japan, is discussed in the light of the new infection concept.

Chronic fatigue syndrome: an update.

Komaroff AL, Buchwald DS. Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.

Annu Rev Med 1998;49:1-13

Among the many patients who seek medical care for the complaint of fatigue, a small number suffer from chronic fatigue syndrome (CFS). CFS is a poorly understood condition characterized by debilitating fatigue and associated symptoms lasting at least six months. Studies indicate that the illness is not simply a manifestation of an underlying psychiatric disorder, but rather is an illness characterized by activation of the immune system, various abnormalities of several hypothalamic-pituitary axes, and reactivation of certain infectious agents.

Dehydroepiandrosterone sulfate deficiency in chronic fatigue syndrome.

Kuratsune H, Yamaguti K, Sawada M, Kodate S, Machii T, Kanakura Y, Kitani T. Department of Hematology and Oncology, Osaka University Medical School, Suita city, Osaka 565, Japan.

Int J Mol Med 1998 Jan;1(1):143-6

The chronic fatigue syndrome (CFS) is a condition of unknown etiology, characterized by a persistent debilitating fatigue, the muscle-related symptoms and the neuropsychiatric symptoms. Recently, it has been reported that the patients with CFS might have impaired activation of the hypothalamic-pituitary-adrenal axis, and suggested that a part of the patho-genesis of CFS might be associated with abnormalities of the endocrine system. Herein, we show that the majority of Japanese patients with CFS had a serum dehydroepiandrosterone sulfate (DHEA-S) deficiency. Serum DHEA-S is one of the most abundantly produced hormones which is secreted from the adrenal glands, and its physiological function is thought to be a precursor of sex steroids. DHEA-S has recently been shown to have physiological properties, such as neurosteroids, which are associated with such psychophysiological phenomena as memory, stress, anxiety, sleep and depression. Therefore, the deficiency of DHEA-S might be related to the neuropsychiatric symptoms in patients with CFS.

Stabilium and chronic fatigue. The positive role of a neutraceutical in memory and cognitive function and symptoms of chronic fatigue in adults.

Le Poncin, M., Pallier, E., Elbaz, H.

Focus 2000 Winter. Hayward, CA: Allergy Research Center.

Chronic fatigue syndrome: oxidative stress and dietary modifications.

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Altern Med Rev 2001 Oct;6(5):450-9

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; however, a number of recent studies have shown oxidative stress may be involved in its pathogenesis. The role of oxidative stress in CFS is an important area for current and future research as it suggests the use of antioxidants in the management of CFS. Specifically, the dietary supplements glutathione, N-acetylcysteine, alpha-lipoic acid, oligomeric proanthocyanidins, Ginkgo biloba, and Vaccinium myrtillus (bilberry) may be beneficial. In addition, research on food intolerance is discussed, since food intolerance may be involved in CFS symptom presentation and in oxidation via cytokine induction. Finally, recent evidence suggests celiac disease can present with neurological symptoms in the absence of gastrointestinal symptoms; therefore, celiac disease should be included in the differential diagnosis of CFS.

Simultaneous measurement of antibodies to Epstein-Barr virus, human herpesvirus 6, herpes simplex virus types 1 and 2, and 14 enteroviruses in chronic fatigue syndrome: is there evidence of activation of a nonspecific polyclonal immune response?

Manian FA. Division of Infectious Diseases, St. John's Mercy Medical Center, St. Louis, Missouri.

Clin Infect Dis 1994 Sep;19(3):448-53

As a test of the hypothesis that elevated titers of viral antibodies in patients with chronic fatigue syndrome (CFS) are due to a nonspecific polyclonal immune response, antibodies to Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), and 14 enteroviruses in 20 patients with CFS and 20 age- and gender-matched controls were simultaneously measured. Similarly, titers of IgG to herpes simplex virus (HSV) types 1 and 2 were measured in 18 of these cases and in the respective controls. IgG to EBV viral capsid antigen (VCA) was present at titers $\leq 1:320$ in 55% of cases vs. 15% of controls ($P = .02$). The geometric mean titers of early antigen antibody to EBV, HHV-6 IgG, and HSV-1 and HSV-2 IgG were not significantly different among cases and controls. Of the 14 enteroviral antibodies tested for, only those to coxsackieviruses B1 and B4 were present at significant titers ($\leq 1:8$) in cases vs. controls ($P = .02$ and $P = .001$, respectively). Of the cases, 19 (95%) had either an EBV VCA IgG titer $\leq 1:320$ or a coxsackievirus B1 or B4 antibody titer $\leq 1:8$, a percentage significantly higher than that of controls (40%; $P = .0004$). Titers of EBV VCA IgG and coxsackievirus B1 and B4 antibodies were simultaneously elevated in only 20% of cases. There was no correlation between elevated titers of EBV VCA IgG and IgG to HHV-6, HSV-1, and HSV-2 or antibody to coxsackieviruses B1 and B4 in the cases. The prevalence of reported allergies to medications or other substances was identical in both groups (60%). These findings suggest that in the majority of cases of CFS, elevation of viral antibody titers is not due to a nonspecific polyclonal immune response.

Magnesium status and parameters of the oxidant-antioxidant balance in patients with chronic fatigue: effects of supplementation with magnesium.

Manuel y Keenoy B, Moorkens G, Vertommen J, Noe M, Neve J, De Leeuw I. Laboratory of Endocrinology, University of Antwerp, Belgium.

J Am Coll Nutr 2000 Jun;19(3):374-82

OBJECTIVE: Magnesium deficiency and oxidative stress have both been identified as pathogenic factors in aging and in several age-related diseases. The link between these two factors is unclear in humans although, in experimental animals, severe Mg deficiency has been shown to lead to increased oxidative stress. **METHODS:** The relationship between Mg body stores, dietary intakes and supplements on the one hand and parameters of the oxidant-antioxidant balance on the other was investigated in human subjects. **RESULTS:** The study population consisted of 93 patients with unexplained chronic fatigue (median age 38 years, 25% male, 16% smokers and 54% with Chronic Fatigue Syndrome (CFS). Mg deficient patients (47%) had lower total antioxidant capacity in plasma ($p=0.007$) which was related to serum albumin. Mg deficient patients whose Mg body stores did not improve after oral supplementation with Mg (10 mg/kg/day) had persistently lower blood glutathione levels ($p=0.003$). In vitro production of thiobarbituric acid reactive substances (TBARS) by non-HDL lipoproteins incubated with copper was related to serum cholesterol (< 0.001) but not to Mg or antioxidants and did not improve after Mg supplementation. In contrast, velocity of formation of fluorescent products of peroxidation (slope) correlated with serum vitamin E (< 0.001), which was, in turn, related to Mg dietary intakes. Both slope and serum vitamin E improved after Mg supplementation (< 0.001). **CONCLUSIONS:** These results show that the lower antioxidant capacity found in moderate Mg deficiency was not due to a deficit in Mg dietary intakes and was not accompanied by increased lipid susceptibility to in vitro peroxidation. Nevertheless, Mg supplementation was followed by an improvement in Mg body

stores, in serum vitamin E and its interrelated stage of lipid peroxidation.

Antioxidant status and lipoprotein peroxidation in chronic fatigue syndrome.

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Life Sci 2001 Mar 16;68(17):2037-49

The aetiology and pathogenesis of the Chronic Fatigue Syndrome (CFS) are still largely unresolved. Accompanying metabolic disorders such as selective n-6 fatty acid depletion suggest that oxidative stress and more specifically lipid peroxidation might play a role in its pathogenesis. In order to investigate this hypothesis, oxidant-antioxidant status and its impact on lipoprotein peroxidation in vitro was examined in 61 patients with unexplained fatigue lasting more than 1 month. They were subdivided into 2 groups: group CFS+ (33 subjects) fulfilled the 1988 Center of Disease Control criteria for CFS and group CFS- did not but was similar as regards age, sex distribution and clinical characteristics. Antioxidant status was similar in the 2 groups except for lower serum transferrin in the CFS + (mean (95 % CI) 2.41 (2.28-2.54) versus 2.73 (2.54-2.92) g/L in the CFS-, $p = 0.009$) and higher lipoprotein peroxidation in vitro: 6630 (5949-7312) versus 5581 (4852-6310) nmol MDA/mg LDL and VLDL cholesterol x minutes, $p = 0.035$). CFS intensified the influence of LDL cholesterol ($p = 0.012$) and of transferrin ($p = 0.045$) on peroxidation in vitro, suggesting additional pro-oxidant effects. These results indicate that patients with CFS have increased susceptibility of LDL and VLDL to copper-induced peroxidation and that this is related both to their lower levels of serum transferrin and to other unidentified pro-oxidising effects of CFS.

Reduced oxidative muscle metabolism in chronic fatigue syndrome.

McCully KK, Natelson BH, Iotti S, Sisto S, Leigh JS Jr. Department of Medicine, Medical College of Pennsylvania, Philadelphia 19131, USA.

Muscle Nerve 1996; 19(5): 621-5.

The purpose of this study was to determine if chronic fatigue syndrome (CSF) is characterized by abnormalities in oxidative muscle metabolism. Patients with CFS according to Centers for Disease Control (CDC) criteria ($n = 22$) were compared to normal sedentary subjects ($n = 15$). CFS patients were also tested before and 2 days after a maximal treadmill test. Muscle oxidative capacity was measured as the maximal rate of postexercise phosphocreatine (PCr) resynthesis using the ADP model (V_{max}) in the calf muscles using ^{31}P magnetic resonance spectroscopy. V_{max} was significantly reduced in CFS patients (39.6 ± 2.8 mmol/L/min, mean \pm SE) compared to controls (53.8 ± 2.8 mmol/L/min). Two days postexercise there was no change in resting inorganic phosphate (P_i)/PCr or V_{max} in the CFS patients ($n = 14$). In conclusion, oxidative metabolism is reduced in CFS patients compared to sedentary controls. In addition, a single bout of strenuous exercise did not cause a further reduction in oxidative metabolism, or alter resting P_i /PCr ratios.

Impaired oxygen delivery to muscle in chronic fatigue syndrome.

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Clin Sci (Lond) 1999 Nov;97(5):603-8; discussion 611-3

The purpose of this study was to determine if chronic fatigue syndrome (CFS) is associated with reduced oxygen delivery to muscles. Patients with CFS according to CDC (Center for Disease Control) criteria ($n=20$) were compared with normal sedentary subjects ($n=12$). Muscle oxygen delivery was measured as the rate of post-exercise and post-ischaemia oxygen-haem resaturation. Oxygen-haem resaturation was measured in the medial gastrocnemius muscle using continuous-wavelength near-IR spectroscopy. Phosphocreatine resynthesis was measured simultaneously using (^{31}P) magnetic resonance spectroscopy. The time constant of oxygen delivery was significantly reduced in CFS patients after exercise (46.5 ± 16 s; mean \pm S.D.) compared with that in controls (29.4 ± 6.9 s). The time constant of oxygen delivery was also reduced (20.0 ± 12 s) compared with controls (12.0 ± 2.8 s) after cuff ischaemia. Oxidative metabolism was also reduced by 20% in CFS patients, and a significant correlation was found between oxidative metabolism and recovery of oxygen delivery. In conclusion, oxygen delivery was reduced in CFS patients compared with that in sedentary controls. This result is consistent with previous studies showing abnormal autonomic control of blood flow. Reduced oxidative delivery in CFS patients could be specifically related to CFS, or could be a non-specific effect of reduced activity levels in these patients. While these results suggest that reduced oxygen delivery could result in reduced oxidative metabolism and muscle fatigue, further studies will be needed to address this issue.

Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome.

Rheum Dis Clin North Am 2000 Nov;26(4):989-1002

A large body of data from a number of different laboratories worldwide has demonstrated a general tendency for reduced adrenocortical responsiveness in CFS. It is still not clear if this is secondary to CNS abnormalities leading to decreased activity of CRH- or AVP-producing hypothalamic neurons. Primary hypofunction of the CRH neurons has been described on the basis of genetic and environmental influences. Other pathways could secondarily influence HPA axis activity, however. For example, serotonergic and noradrenergic input acts to stimulate HPA axis activity. Deficient serotonergic activity in CFS has been suggested by some of the studies as reviewed here. In addition, hypofunction of sympathetic nervous system function has been described and could contribute to abnormalities of central components of the HPA axis. One could interpret the clinical trial of glucocorticoid replacement in patients with CFS as confirmation of adrenal insufficiency if one were convinced of a positive therapeutic effect. If patient symptoms were related to impaired activation of central components of the axis, replacing glucocorticoids would merely exacerbate symptoms caused by enhanced negative feedback. Further study of specific components of the HPA axis should ultimately clarify the reproducible abnormalities associated with a clinical picture of CFS. In contrast to CFS, the results of the different hormonal axes in FMS support the assumption that the distortion of the hormonal pattern observed can be attributed to hyperactivity of CRH neurons. This hyperactivity may be driven and sustained by stress exerted by chronic pain originating in the musculoskeletal system or by an alteration of the CNS mechanism of nociception. The elevated activity of CRH neurons also seems to cause alteration of the set point of other hormonal axes. In addition to its control of the adrenal hormones, CRH stimulates somatostatin secretion at the hypothalamic level, which, in turn, causes inhibition of growth hormone and thyroid-stimulating hormone at the pituitary level. The suppression of gonadal function may also be attributed to elevated CRH because of its ability to inhibit hypothalamic luteinizing hormone-releasing hormone release; however, a remote effect on the ovary by the inhibition of follicle-stimulating hormone-stimulated estrogen production must also be considered. Serotonin (5-HT) precursors such as tryptophan (5-HTP), drugs that release 5-HT, or drugs that act directly on 5-HT receptors stimulate the HPA axis, indicating a stimulatory effect of serotonergic input on HPA axis function. Hyperfunction of the HPA axis could also reflect an elevated serotonergic tone in the CNS of FMS patients. The authors conclude that the observed pattern of hormonal deviations in patients with FMS is a CNS adjustment to chronic pain and stress, constitutes a specific entity of FMS, and is primarily evoked by activated CRH neurons.

Decreased natural killer cell activity is associated with severity of chronic fatigue immune dysfunction syndrome.

Ojo-Amaize EA, Conley EJ, Peter JB. Specialty Laboratories, Incorporated, Santa Monica, California 90404.

Clin Infect Dis 1994 Jan;18 Suppl 1:S157-9

Natural killer (NK) cell activity was measured blindly in vitro with blood specimens from 50 healthy individuals and 20 patients with clinically defined chronic fatigue immune dysfunction syndrome (CFIDS) who met the criteria established by the Centers for Disease Control and Prevention (Atlanta). In accordance with a group scoring system of 1-10 points, with 10 being the most severe clinical status, the patient population was stratified into three clinical groups: A (< 7 points), B (5-7 points), and C (< 5 points). NK cell activity was assessed by the number of lytic units (LU), which for the 50 healthy controls varied between 20 and 250 (50%, 20-50 LU; 32%, 51-100 LU; 6%, 101-130 LU; and 12%, < 150 LU). In none of the 20 patients with CFIDS was the NK cell activity < 100 LU. For group C, the 10 patients stratified as having the least severe clinical condition, the measure was 61.0 +/- 21.7 LU; for group B (more severe, n = 7), it was 18.3 +/- 7.3 LU; and for group A (most severe, n = 3), it was 8.0 +/- 5.3 LU. These data suggest a correlation between low levels of NK cell activity and severity of CFIDS, which, if it is confirmed by additional studies of larger groups, might be useful for subgrouping patients and monitoring therapy and/or the progression of CFIDS.

Tyrosine and its potential use as a countermeasure to performance decrement in military sustained operations.

Owasoyo JO, Neri DF, Lamberth JG. Naval Aerospace Medical Research Laboratory, Pensacola, FL.

Aviat Space Environ Med 1992 May;63(5):364-9

We review the biochemistry and physiological role of the amino acid tyrosine in normal and stressful situations such as military sustained operations. Sustained operations consist of continuous work periods exceeding 12 h and often involve sleep loss and fatigue. These, in turn, can lead to stress, anxiety, mood deterioration, and performance decrement. Experimental data in the literature suggest that tyrosine, a precursor of the neurotransmitter norepinephrine, may be useful in counteracting any stress-related performance decrement and mood deterioration in the following way. First, various forms of stress induce brain depletion of catecholamines, especially norepinephrine, in animals. Second, brain norepinephrine levels are closely related to stress-induced performance decrement in animals. Third, the administration of tyrosine may minimize or reverse stress-induced performance decrement by increasing depleted brain norepinephrine levels. The types of performance degradation expected in military sustained

operations and the potential physiological role tyrosine might play in improving mood and performance are discussed.

Elevated, sustained peroxynitrite levels as the cause of chronic fatigue syndrome.

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Med Hypotheses 2000 Jan;54(1):115-25

The etiology of chronic fatigue syndrome (CFS) has been both obscure and highly contentious, leading to substantial barriers to both clear diagnosis and effective treatment. I propose here a novel hypothesis of CFS in which either viral or bacterial infection induces one or more cytokines, IL-1beta IL-6, TNF-alpha and IFN-gamma. These induce nitric oxide synthase (iNOS), leading to increased nitric oxide levels. Nitric oxide, in turn, reacts with superoxide radical to generate the potent oxidant peroxynitrite. Multiple amplification and positive feedback mechanisms are proposed by which once peroxynitrite levels are elevated, they tend to be sustained at a high level. This proposed mechanism may lower the HPA axis activity and be maintained by consequent lowered glucocorticoid levels. Similarities are discussed among CFS and autoimmune and other diseases previously shown to be associated with elevated peroxynitrite. Multiple pharmacological approaches to the treatment of CFS are suggested by this hypothesis.

Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite.

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Med Hypotheses 2001 Aug;57(2):139-45

Three types of overlap occur among the disease states chronic fatigue syndrome (CFS), fibromyalgia (FM), multiple chemical sensitivity (MCS) and posttraumatic stress disorder (PTSD). They share common symptoms. Many patients meet the criteria for diagnosis for two or more of these disorders and each disorder appears to be often induced by a relatively short-term stress which is followed by a chronic pathology, suggesting that the stress may act by inducing a self-perpetuating vicious cycle. Such a vicious cycle mechanism has been proposed to explain the etiology of CFS and MCS, based on elevated levels of nitric oxide and its potent oxidant product, peroxynitrite. Six positive feedback loops were proposed to act such that when peroxynitrite levels are elevated, they may remain elevated. The biochemistry involved is not highly tissue-specific, so that variation in symptoms may be explained by a variation in nitric oxide/peroxynitrite tissue distribution. The evidence for the same biochemical mechanism in the etiology of PTSD and FM is discussed here, and while less extensive than in the case of CFS and MCS, it is nevertheless suggestive. Evidence supporting the role of elevated nitric oxide/peroxynitrite in these four disease states is summarized, including induction of nitric oxide by common apparent inducers of these disease states, markers of elevated nitric oxide/peroxynitrite in patients and evidence for an inductive role of elevated nitric oxide in animal models. This theory appears to be the first to provide a mechanistic explanation for the multiple overlaps of these disease states and it also explains the origin of many of their common symptoms and similarity to both Gulf War syndrome and chronic sequelae of carbon monoxide toxicity. This theory suggests multiple studies that should be performed to further test this proposed mechanism. If this mechanism proves central to the etiology of these four conditions, it may also be involved in other conditions of currently obscure etiology and criteria are suggested for identifying such conditions. Copyright 2001 Harcourt Publishers Ltd.

The neuroendocrinology of chronic fatigue syndrome and fibromyalgia.

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Psychol Med 2001 Nov;31(8):1331-45

BACKGROUND: Disturbance of the HPA axis may be important in the pathophysiology of chronic fatigue syndrome (CFS) and fibromyalgia. Symptoms may be due to: (1) low circulating cortisol; (2) disturbance of central neurotransmitters; or (3) disturbance of the relationship between cortisol and central neurotransmitter function. Accumulating evidence of the complex relationship between cortisol and 5-HT function, make some form of hypothesis (3) most likely. We review the methodology and results of studies of the HPA and other neuroendocrine axes in CFS. **METHOD:** Medline, Embase and Psychlit were searched using the Cochrane Collaboration strategy. A search was also performed on the King's College CFS database, which includes over 3000 relevant references, and a citation analysis was run on the key paper (Demitrack et al. 1991). **RESULTS:** One-third of the studies reporting baseline cortisol found it to be significantly low, usually in one-third of patients. Methodological differences may account for some of the varying results. More consistent is the finding of reduced HPA function, and enhanced 5-HT function on neuroendocrine challenge tests. The opioid system, and arginine vasopressin (AVP) may also be abnormal, though the growth

hormone (GH) axis appears to be intact, in CFS. CONCLUSIONS: The significance of these changes, remains unclear. We have little understanding of how neuroendocrine changes relate to the experience of symptoms, and it is unclear whether these changes are primary, or secondary to behavioural changes in sleep or exercise. Longitudinal studies of populations at risk for CFS will help to resolve these issues.

Serum levels of carnitine in chronic fatigue syndrome: clinical correlates.

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Neuropsychobiology 1995;32(3):132-8

Carnitine is essential for mitochondrial energy production. Disturbance in mitochondrial function may contribute to or cause the fatigue seen in chronic fatigue syndrome (CFS) patients. One previous investigation has reported decreased acylcarnitine levels in 38 CFS patients. We investigated 35 CFS patients (27 females and 8 males); our results indicate that CFS patients have statistically significantly lower serum total carnitine, free carnitine and acylcarnitine levels, not only lower acylcarnitine levels as previously reported. We also found a statistically significant correlation between serum levels of total and free carnitine and clinical symptomatology. Higher serum carnitine levels correlated with better functional capacity. These findings may be indicative of mitochondrial dysfunction, which may contribute to or cause symptoms of fatigue in CFS patients.

Amantadine and L-carnitine treatment of Chronic Fatigue Syndrome.

Plioplys AV, Plioplys S. Chronic Fatigue Syndrome Center, Department of Research, Mercy Hospital Chicago, Ill 60616, USA.

Neuropsychobiology 1997;35(1):16-23

Carnitine is essential for mitochondrial energy production. Disturbance in mitochondrial function may contribute to or cause the fatigue seen in Chronic Fatigue Syndrome (CFS) patients. Previous investigations have reported decreased carnitine levels in CFS. Orally administered L-carnitine is an effective medicine in treating the fatigue seen in a number of chronic neurologic diseases. Amantadine is one of the most effective medicines for treating the fatigue seen in multiple sclerosis patients. Isolated reports suggest that it may also be effective in treating CFS patients. Formal investigations of the use of L-carnitine and amantadine for treating CFS have not been previously reported. We treated 30 CFS patients in a crossover design comparing L-carnitine and amantadine. Each medicine was given for 2 months, with a 2-week washout period between medicines. L-Carnitine or amantadine was alternately assigned as first medicine. Amantadine was poorly tolerated by the CFS patients. Only 15 were able to complete 8 weeks of treatment, the others had to stop taking the medicine due to side effects. In those individuals who completed 8 weeks of treatment, there was no statistically significant difference in any of the clinical parameters that were followed. However, with L-carnitine we found statistically significant clinical improvement in 12 of the 18 studied parameters after 8 weeks of treatment. None of the clinical parameters showed any deterioration. The greatest improvement took place between 4 and 8 weeks of L-carnitine treatment. Only 1 patient was unable to complete 8 weeks of treatment due to diarrhea. L-Carnitine is a safe and very well tolerated medicine which improves the clinical status of CFS patients. In this study we also analyzed clinical and laboratory correlates of CFS symptomatology and improvement parameters.

Exercise training-induced alterations in skeletal muscle antioxidant capacity: a brief review.

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Med Sci Sports Exerc 1999 Jul;31(7):987-97

Cellular oxidants include a variety of reactive oxygen, nitrogen, and chlorinating species. It is well established that the increase in metabolic rate in skeletal muscle during contractile activity results in an increased production of oxidants. Failure to remove these oxidants during exercise can result in significant oxidative damage of cellular biomolecules. Fortunately, regular endurance exercise results in adaptations in the skeletal muscle antioxidant capacity, which protects myocytes against the deleterious effects of oxidants and prevents extensive cellular damage. This review discusses the effects of chronic exercise on the up-regulation of both antioxidant enzymes and the glutathione antioxidant defense system. Primary antioxidant enzymes superoxide dismutase, glutathione peroxidase, and catalase will be discussed as well as glutathione, which is an important nonenzymatic antioxidant. Growing evidence indicates that exercise training results in an elevation in the activities of both superoxide dismutase and glutathione peroxidase along with increased cellular concentrations of glutathione in skeletal muscles. It seems plausible that increased cellular concentrations of these antioxidants will reduce the risk of cellular injury, improve performance, and delay muscle fatigue.

Inhibition of mitochondrial electron transport by peroxynitrite.

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Arch Biochem Biophys 1994 Jan;308(1):89-95

Mammalian mitochondria are sensitive targets of the cytotoxic effects of superoxide (O₂⁻) and nitric oxide (.NO). In turn, when superoxide and nitric oxide are simultaneously produced, they rapidly react with each other yielding the highly oxidizing peroxynitrite anion (ONOO⁻) which may be also toxic to mammalian mitochondria. In this study we report that peroxynitrite exposure to rat heart mitochondria resulted in significant inactivation of electron carriers such as succinate dehydrogenase and NADH dehydrogenase as well as the mitochondrial ATPase. As a result of enzyme inactivation, peroxynitrite lead to a profound inhibition of glutamate/malate- and succinate-supported oxygen consumption but did not cause mitochondrial uncoupling. Secondary to inhibiting mitochondrial electron transport, peroxynitrite induced an enhanced succinate-stimulated hydrogen peroxide formation by heart mitochondria. Most of the damaging effects against mitochondria can be ascribed to peroxynitrite anion itself and not to hydroxyl radical-like oxidant yielded during the proton-catalyzed decomposition of peroxynitrite, as hydroxyl radical scavengers provided a rather modest protection. Our observations indicate that mitochondria may constitute a key intracellular loci for the toxic effects of peroxynitrite under the various pathological conditions in which peroxynitrite appears to play a contributory role.

Increased concentrations of homocysteine in the cerebrospinal fluid in patients with fibromyalgia and chronic fatigue syndrome.

Regland B, Andersson M, Abrahamsson L, Bagby J, Dyrehag LE, Gottfries CG. Institute of Clinical Neuroscience, Goteborg University, Sweden.

Scand J Rheumatol 1997;26(4):301-7

Twelve outpatients, all women, who fulfilled the criteria for both fibromyalgia and chronic fatigue syndrome were rated on 15 items of the Comprehensive Psychopathological Rating Scale (CPRS-15). These items were chosen to constitute a proper neurasthenic subscale. Blood laboratory levels were generally normal. The most obvious finding was that, in all the patients, the homocysteine (HCY) levels were increased in the cerebrospinal fluid (CSF). There was a significant positive correlation between CSF-HCY levels and fatiguability, and the levels of CSF-B12 correlated significantly with the item of fatiguability and with CPRS-15. The correlations between vitamin B12 and clinical variables of the CPRS-scale in this study indicate that low CSF-B12 values are of clinical importance. Vitamin B12 deficiency causes a deficient remethylation of HCY and is therefore probably contributing to the increased homocysteine levels found in our patient group. We conclude that increased homocysteine levels in the central nervous system characterize patients fulfilling the criteria for both fibromyalgia and chronic fatigue syndrome.

Chronic fatigue syndrome.

Reid S, Chalder T, Cleare A, Hotopf M, Wessely S.

Br. Med. J. 2000; 320(7230): 292-6.

No abstract available.

Blood parameters indicative of oxidative stress are associated with symptom expression in chronic fatigue syndrome.

Richards RS, Roberts TK, McGregor NR, Dunstan RH, Butt HL. Department of Biological Sciences, University of Newcastle, Australia.

Redox Rep 2000;5(1):35-41

Full blood counts, ESR, CRP, haematinics and markers for oxidative stress were measured for 33 patients diagnosed with chronic fatigue syndrome (CFS) and 27 age and sex matched controls. All participants also completed symptom questionnaires. CFS patients had increases in malondialdehyde (< 0.006), methaemoglobin (< 0.02), mean erythrocyte volume (< 0.02) and 2,3-diphosphoglycerate (< 0.04) compared with controls. Multiple regression analysis found methaemoglobin to be the principal component that differentiated between CFS patients and control subjects. Methaemoglobin was found to be the major component associated with variation in symptom expression in CFS patients ($R(2) = 0.99$, < 0.00001), which included fatigue, musculoskeletal symptoms, pain and sleep disturbance. Variation in levels of malondialdehyde and 2,3-diphosphoglycerate were associated with variations in cognitive symptoms and sleep disturbance ($R(2) = 0.99$, < 0.00001). These data suggest that oxidative stress due to excess free radical formation is a contributor to the pathology of CFS and was associated with symptom presentation.

Differences in adrenal steroid profile in chronic fatigue syndrome, in depression and in health.

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J Affect Disord 1999 Jul;54(1-2):129-37

BACKGROUND: Hyperactivity and hypoactivity of the HPA have been forwarded as of pathophysiological relevance in major depressive disorder and chronic fatigue syndrome (CFS), respectively. **METHODS:** This study examines cortisol levels in the two disorders, and also assesses levels of the adrenal androgens, dehydroepiandrosterone (DHEA) and its sulphate derivative (DHEA-S), and 17-alpha-hydroxyprogesterone; 15 subjects with CFS diagnosed according to CDC criteria, 15 subjects with DSM III-R major depression and 11 healthy subjects were compared. **RESULTS:** DHEA and DHEA-S levels were significantly lower in the CFS compared to the healthy group; DHEA-S levels, but not DHEA, were lower in the depressives; cortisol and 17-alpha-hydroxyprogesterone did not differ between the three groups. **CONCLUSIONS:** A potential role for DHEA, both therapeutically and as a diagnostic tool, in CFS, is suggested.

Metal-specific lymphocytes: biomarkers of sensitivity in man.

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Neuroendocrinol Lett 1999;20(5):289-298

Many patients attribute their health problems to amalgam and other dental metals. In genetically susceptible individuals, mercury and gold may function as haptens and elicit allergic and autoimmune reactions. The frequency of metal-induced lymphocyte responses was examined in 3,162 patients in three European laboratories using MELISA(R), an optimized lymphocyte proliferation test. The patients suffered from local and systemic symptoms attributed to dental restorations. The effect of dental metal removal was studied in 111 patients with metal hypersensitivity and symptoms resembling Chronic Fatigue Syndrome (CFS). After consultation with a dentist the patients decided to replace their metal restorations with non-metallic materials. The changes in health and in vitro lymphocyte reactivity were studied by inquiries and follow-up MELISA(R). Lymphocyte reactivity was also analyzed in 116 healthy subjects with no complaints of metal allergy. A significant number of patients had metal-specific lymphocytes in the blood. Nickel was the most common sensitizer, followed by inorganic mercury, gold, phenylmercury, cadmium and palladium. As compared to lymphocyte responses in healthy subjects, the CFS group had significantly increased responses to several metals, especially to inorganic mercury, phenylmercury and gold. Following dental metal removal, 83 patients (76%) reported long-term health improvement. Twenty-four patients (22%) reported unchanged health and two (2%) reported worsening of symptoms. Following dental metal replacement, the lymphocyte reactivity to metals decreased as well. We propose that an inflammatory process induced by metals may modulate the hypothalamic-pituitary-adrenal axis (HPA axis) and trigger multiple non-specific symptoms characterizing CFS and other chronic conditions like myalgic encephalitis (ME) and multiple chemical sensitivity (MCS).

How to manage anxious patients who are depressed.

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J Clin Psychiatry 1993 May;54 Suppl:8-16; discussion 17-20

According to the official nomenclature and the approved indications for psychotropic drugs, anxiety and depression are mutually exclusive, and antidepressants and anxiolytics have a single indication. In clinical settings, however, anxiety and depressive symptoms frequently coexist, and the effects of psychotropic drugs often overlap. Both diagnosis and treatment may be complicated by uncertainty about the primary disorder and the optional therapeutic approach. Available treatment strategies include antidepressants, benzodiazepines, azapirones, and combined antidepressant/anxiolytic therapy. Considerations in reflecting a particular treatment strategy include drug side effects, patient age and medical status, and patient expectations. Recent studies have suggested that antidepressants are effective anxiolytics and that some anxiolytics produce antidepressant effects. Ultimately, any selection should be made based on relative benefits and risks of each approach.

Treating anxiety while minimizing abuse and dependence.

Sussman N. Department of Psychiatry, New York University Medical Center, N.Y.

J Clin Psychiatry 1993 May;54 Suppl:44-51

Anxiety is common and often disabling. Although effective treatments are available, the use of antianxiety medication remains

controversial. Some of the concerns involve the relative benefits of psychological versus pharmacologic interventions. Much of the expressed concern, however, relates to the risks of abuse and dependence associated with standard anti-anxiety drugs. In some instances, concern about these risks prevents patients from receiving potentially effective treatment. In other instances, failure to recognize possible abuse and dependence results in a clinical dilemma. This presentation will address the factors involved in anxiolytic drug dependence and abuse, including patient characteristics and the pharmacologic profiles of anxiolytic drugs. Specific recommendations about how to minimize abuse and dependence through such measures as diagnostic assessment, patient education, drug selection, and treatment planning will be offered.

The three-way interactions between the hypothalamic-pituitary-adrenal and gonadal axes and the immune system.

Torpy DJ, Chrousos GP. Developmental Endocrinology Branch, National Institute of Child Health and Human Development, Bethesda, MD 20892, USA.

Baillieres Clin Rheumatol 1996 May;10(2):181-98

The stress system is controlled by brain nuclei at the hypothalamus and brainstem. These nuclei interact with each other and control the HPA axis and sympathetic nervous systems, respectively. Major inputs to the stress system arise from the cerebral cortex and subcortical systems, the sensory organs and nerves, and the endocrine and immune systems. The major peripheral effectors of the stress system are glucocorticoids and the catecholamines. Pathological hypoactivity of the stress system has been associated with atypical depression, the chronic fatigue/fibromyalgia syndromes and autoimmune inflammatory disease; hyperactivity with melancholic depression and anxiety disorders. The stress system responds in a quantitatively and qualitatively specific fashion to different stressors. A major role of the HPA axis is to restrain the immune system and prevent tissue damage. Reciprocal interactions between the HPA axis and immune system constitutes a new endocrine feedback loop that has given rise to the field of neuroendocrine immunology. Gonadal axis hormones directly, and indirectly via the HPA axis, alter the tone of the immune system and the quality and quantity of the inflammatory responses. Effects of the HPA axis on the gonadal axis are consistent with conservation and redirection of valuable resources towards homeostasis during times of stress. These complex interactions between the HPA axis, immune and the gonadal systems may prove to be fundamental in the genesis and perpetuation of autoimmune disease.

Chronic Fatigue Syndrome 1997.

Verillo, E.F., Gellman, L.M.

New York: St Martin's/Griffin.

The role of essential fatty acids in chronic fatigue syndrome. A case-controlled study of red-cell membrane essential fatty acids (EFA) and a placebo-controlled treatment study with high dose of EFA.

Warren G, McKendrick M, Peet M. The University of Sheffield, Section of Psychiatry, Northern General Hospital, UK.

Acta Neurol Scand 1999 Feb;99(2):112-6

OBJECTIVE: To replicate the treatment study by Behan et al. (1990) using current research criteria for Chronic Fatigue Syndrome (CFS). **METHOD:** Fifty patients who fulfilled the Oxford Criteria for CFS were randomly allocated to treatment with either Efamol Marine or placebo for 3 months. They were seen monthly and completed a physical symptoms checklist and the Beck Inventory for Depression and reported if they were the same, better or worse at the end of the study. **RESULTS:** Symptoms generally improved with time but not significantly and there were no significant differences between the treatment and placebo groups. Pretreatment red-cell membrane (RBC) lipids of patients compared with age- and sex-matched normal controls showed no significant differences. **DISCUSSION:** The results of this study contrast sharply with the previous study where 85% of patients had a clinically significant improvement of symptoms with Efamol Marine over a 3-month treatment period.

Nutritional strategies for treating chronic fatigue syndrome.

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Altern Med Rev 2000 Apr;5(2):93-108

Despite considerable worldwide efforts, no single etiology has been identified to explain the development of chronic fatigue syndrome (CFS). It is likely that multiple factors promote its development, sometimes with the same factors both causing and being caused by the syndrome. A detailed review of the literature suggests a number of marginal nutritional deficiencies may have etiologic relevance. These include deficiencies of various B vitamins, vitamin C, magnesium, sodium, zinc, L-tryptophan, L-carnitine,

coenzyme Q10, and essential fatty acids. Any of these nutrients could be marginally deficient in CFS patients, a finding that appears to be primarily due to the illness process rather than to inadequate diets. It is likely that marginal deficiencies not only contribute to the clinical manifestations of the syndrome, but also are detrimental to the healing processes. Therefore, when feasible, objective testing should identify them and their resolution should be assured by repeat testing following initiation of treatment. Moreover, because of the rarity of serious adverse reactions, the difficulty in ruling out marginal deficiencies, and because some of the therapeutic benefits of nutritional supplements appear to be due to pharmacologic effects, it seems rational to consider supplementing CFS patients with the nutrients discussed above, along with a general high-potency vitamin/mineral supplement, at least for a trial period.

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