Systemic Exertion Intolerance Disease/Chronic Fatigue Syndrome-A Naturopathic Route To Resolution

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AARM
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Disclosures

- Born Naturopathic Associates, Inc.
  - Co-owner and medical director.
- Allergy Research Group LLC
  - Director of new product development, product manager and editor-in-chief of Focus Newsletter.
  - Clinical Education
    - Thought Leader
- International Society for Naturopathic Medicine
  - Lead educator and advisor

Terminology & Definitions

- Chronic Fatigue Syndrome
- Myalgic Encephalomyelitis (UK)
- Chronic Multifactorial Fatigue (Mayo Clinic)
- 2015 Institute of Medicine (IOM)
  - Redefined diagnostic criteria and suggested name change to Systemic Exertion Intolerance Disease (SEID)

Diagnostic Criteria

Symptoms should be present for at least six months and have moderate, substantial, or severe intensity at least one-half of the time.

2015 IOM diagnostic criteria for CFS/SEID

Diagnosis requires that the patient have the following three symptoms:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than six months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest; and
2. Post-exertional malaise;* and
3. Unrefreshing sleep*

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance±

* Frequency and severity of symptoms should be assessed. The diagnosis of CFS/SEID should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.
± Onset of symptoms when standing upright that are improved by lying back down

From: Institute of Medicine of the National Academies. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an illness. Report Brief, February 2015. Reprinted with permission from the National Academies Press, Copyright © 2015 National Academy of Sciences.

CDC Diagnostic Criteria

- The fatigue of CFS is accompanied by characteristic illness symptoms lasting at least 6 months. These symptoms include:
  - increased malaise (extreme exhaustion and sickness) following physical activity or mental exertion
  - problems with sleep
  - difficulties with memory and concentration
  - persistent muscle pain
  - arthralgias (without redness or swelling)
  - headache
  - Cervical or axillary tender lymph nodes
  - pharyngitis

Epidemiology

- Prospective cohort study of over 4000 patients in a health maintenance

Signs and Symptoms

- Relatively sudden onset of fatigue.
  - Often associated with a typical infection such as an URI or true mononucleosis.
- The patient has overwhelming fatigue and a number of additional symptoms, especially altered sleep and cognition.
- Excessive physical activity characteristically exacerbates the symptoms.
- Affected patients are typically highly functioning individuals who are "struck down" with the disease. There is often, however, a history of psychiatric disorders.

Katon WJ, et al. Psychiatric illness in patients with chronic fatigue and those with rheumatoid arthritis. J Gen Intern Med. 1991;6(4):277.

Lante TJ, et al. Depression and somatization in the chronic fatigue syndrome. Am J Med. 1991;91(4):335.

Diagnostic Difficulty

- Once the inciting illness (if any) is resolved, PE typically is normal.
- Although patients commonly feel febrile, few ever demonstrate elevated temps (po greater than 37.40C/99.30F).
- Arthralgias, but no erythema, effusion, or limitation of motion.
- Easily fatigued muscles (PPR), strength is normal, as are biopsies and electromyograms.
- Mild cervical and/or axillary lymphadenitis, along with painful lymph nodes (lymphadenia) are a frequent complaints, but not true lymphadenopathy, is not present.
  - Biopsied lymph nodes show only reactive hyperplasia. The cervical lymph nodes are most commonly involved, but the axillary lymph nodes may also be

Diagnostic Difficulty

- “Routine Labs” typically only elucidate causation in about 5% of cases.
- No specific tests available.
- Many patients are partially or completely disabled by its manifestations.
- The illness has a pattern of remission and relapse.
- Outward healthy appearance doesn’t tell story of how they actually feel.
- Accused of malingerers, worsening their physical and mental symptoms.

Lane TJ. The low yield of physical examinations and laboratory investigations of patients with chronic fatigue. Am J Med Sci. 1990;299(5):313.

SEID/CFS & Fibromyalgia

Approximately 70 percent of patients with fibromyalgia meet the criteria for SEID/CFS.

Clinical similarities between fibromyalgia and systemic exertion intolerance disease (SEID), also known as chronic fatigue syndrome (CFS)

80 to 90% women, usual ages 20 to 55 years
Myalgias and fatigue in more than 90%
Associated common symptoms
Neurocognitive and mood disturbances
Headaches
Sleep disturbances
No identifiable cause
Testing is normal
Physical examination usually normal except for tender points which are required for diagnosis of fibromyalgia and present in most patients with chronic fatigue
Normal laboratory and radiologic tests
Chronic symptoms, no highly effective therapy

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Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med. 1994;154(18):2049.

Proposed Etiologies

- Viruses
  - EBV, HHV-6, CMV, enteroviruses, coxsackie B, Ross River, Borna disease, xenotropic murine leukemia virus-related virus (XMRV), murine leukemia virus (MLV), Mycoplasma, Coxiella burnetti (Q Fever), Rubella…
- Immune Dysfunction compared to healthy controls
  - ↓Immune complexes, NK cells and their function; altered IgG levels and CD4/CD8 ratios.
  - ↑ interferon and cytokine activity & IL-2
- Endocrine-metabolic dysfunction
  - Physical or emotional stress, which is commonly reported as a pre-onset condition in CFS patients, alters the activity of the or HPA axis.

Proposed Etiologies

- Neurally-mediated hypotension (NMH)/Postural Orthostatic Tachycardia (POTS)
  - develop lower blood pressure with tilt table testing, as well as other characteristic symptoms, such as lightheadedness, visual dimming, or a slow response to verbal stimuli.
- Neuropsychiatric factors (2/3 or more meet criteria)
  - Depressive d/o, Anxiety d/o, etc.
- Genetics
  - DNA sequence changes in three genes associated with brain function, stress reactions, and emotional responses led to differences in how the body responds to hormones and other chemical messengers.

Genetics Always at Play

Pharmacogenomics. 2006 Apr;7(3):387-94.

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

Smith AK[1], White PD, Aslakson E, Vollmer-Conna U, Rajeevan MS.

⊕ **Author information**

Abstract

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 polymorphsims 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.

PMID: 16610949 DOI: 10.2217/14622416.7.3.387

Genetics Always at Play

Pharmacogenomics. 2006 Apr;7(3):475-83.

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

Goertzel BN[1], Pennachin C, de Souza Coelho L, Gurbaxani B, Maloney EM, Jones JF.

⊕ Author information

Abstract

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.

PMID: 16610957 DOI: 10.2217/14622416.7.3.475

Other Proposed Etiologies

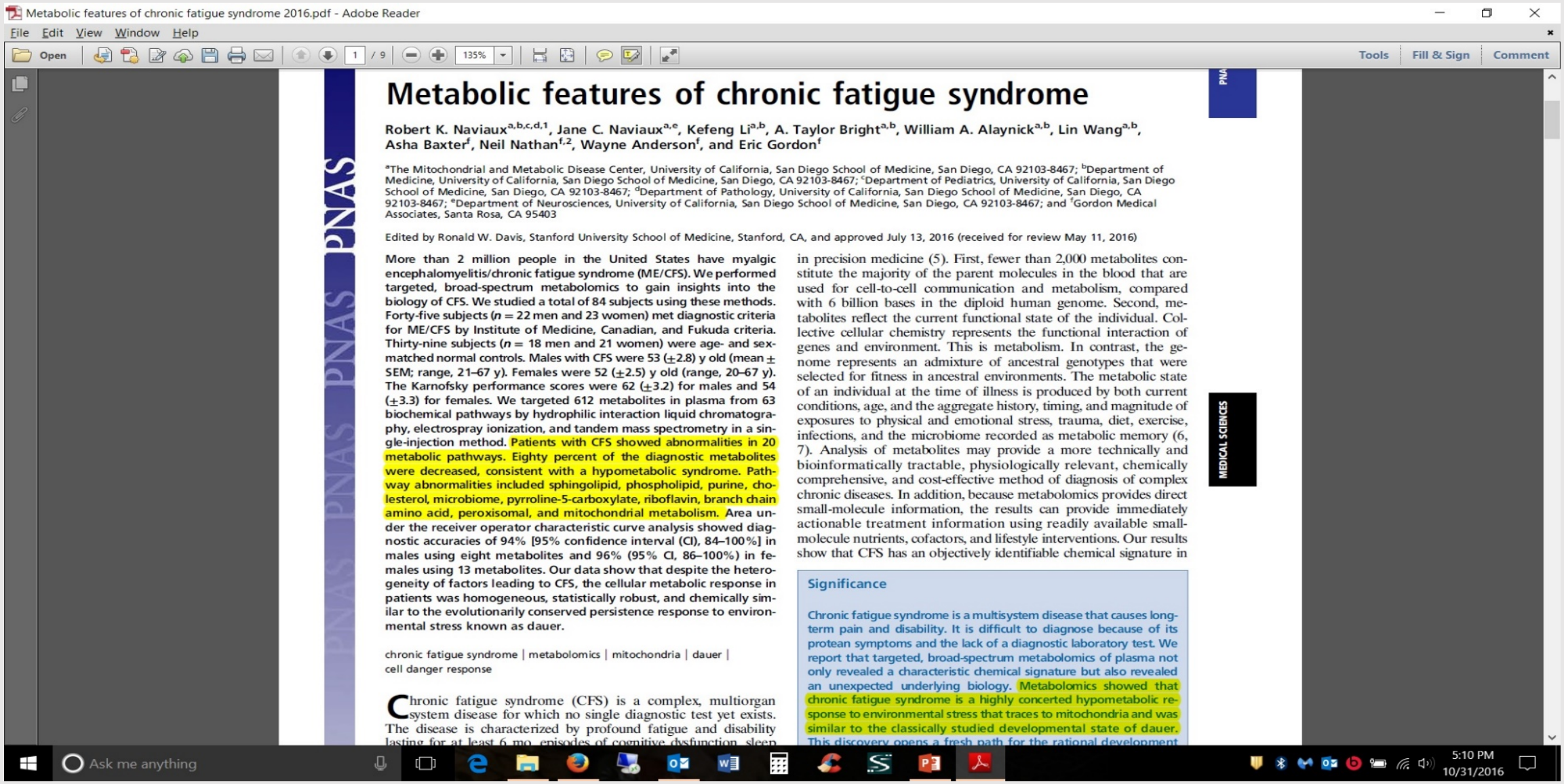
- Mitochondrial dysfunction
  - Major immediate causes of the dysfunction are lack of essential substrates and partial blocking of the translocator protein sites in mitochondria.

Booth NE, et al. Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Int J Clin Exp Med. 2012;5(3):208-20. Epub 2012 Jun 15.

Myhill S, et al. Chronic fatigue syndrome and mitochondrial dysfunction. Int J Clin Exp Med. 2009;2(1):1-16. Epub 2009 Jan 15.

Racciatti D, et al. Chronic fatigue syndrome following a toxic exposure. Sci Total Environ. 2001 Apr 10;270(1-3):27-31.

Metabolomics



Naturopathic Approach to Dx

- Rule out other etiologies of fatigue.
- Look at co-morbidities
  - Fibromyalgia
  - Sleep dysfunction
  - Dysglycemia/Hypoglycemia
  - Psychiatric illness
- Routine Labs
  - CMP, CBC w/ diff, TSH, FT4, FT3, CRP, ESR, creatine kinase, vitamin D, HbA1c.
- Advanced approach
  - Serum methylmalonic acid, serum + RBC magnesium, ionized calcium, iron

EBV Interpretation

Marker	Non-Immune	Primary Infection	Past Infection	Reactivation
VCA IgM	N	P	N	N
VCA IgG	N	P	P	P
EA IgG	N	P	N	P
NA IgG	N	N	P	P

N = negative, P = positive

Patterns not falling within one of the above groupings are Indeterminate and it is recommended the patient be redrawn and retested in 1 month.

Notes: Occasionally a false positive result occurs with specimens containing Abs to HIV. With a positive EBV EA IgG result it is essential to exclude HIV disease.
Approximately 5% to 10% of patients with EBV never develop antibodies to EBNA (past).

Conventional Treatment

- Systematic reviews of SEID/CFS have determined effectiveness for only two treatments: cognitive behavioral therapy (CBT) and graded exercise therapy (GET).
- Antidepressants
- Sleep hygiene
- Support groups
- Iron therapy in nonanemic patients with low serum ferritin.

Price JR, et al. Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD001027.

Whiting P, et al. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. JAMA. 2001;286(11):1360.

Naturopathic Strategies

- Two-thirds of patients with SEID/CFS reported that they were dissatisfied with the quality of their medical care and felt their clinicians lacked communication skills and education regarding their diagnosis.
  - Ergo, support is key.
- Try to find accurate underlying abnormalities and address accordingly.
- Counseling and graded exercise
- Sleep hygiene, if poor sleep present

My Own Clinical Approach

- Hx & PE
  - Look for themes and trends
    - Consider IOM dx, et al criteria.
- Constitutional homeopathy
- Appropriate blood tests (see slide 17)
- Return in 3 weeks for A//
- + EBV, CMV and/or HHV-6
  - **<u>Gemmotherapy</u>**
    - *Acer campestre, Juniperus communis, Tamarix gallica*
  - **Oligoelement**

My Own Clinical Approach

- Potent multivitamin/mineral

  Maric D, et al. Multivitamin mineral supplementation in patients with chronic fatigue syndrome. Med Sci Monit. 2014 Jan 14;20:47-53.

- Prebiotics (XOS, GOS, FOS) & Probiotics, Saccharomyces boulardii

  Lakhan SE & Kirchgessner A. Gut inflammation in chronic fatigue syndrome. Nutr Metab (Lond). 2010 Oct 12;7:79.

  Pothoulakis C. Review article: anti-inflammatory mechanisms of action of Saccharomyces boulardii. Aliment Pharmacol Ther. 2009 Oct 15;30(8):826-33.

- Return in 6 weeks for A//
  - 98% of my patients (over 150 cases so far) are at least 90% better.
    - ***Ribes nigrum* gemmotherapy**
  - For those that aren't substantially better, but responded to therapy, repeat.

My Own Clinical Approach

- 2% non-responders
  - **Antivirals**
    - Acyclovir, Valacyclovir, Famciclovir, Valganciclovir
      - 250 mg-1000 mg, TID-QID
        - Adjust for renal impairment.
  - **Humic acid:** 750-3000 mg qd, in divided doses
    - MOA: interferes with a virus' ability to attach to a host cell, penetrate the host cell, and reproduce itself.

Learner AM, et al. Valacyclovir treatment in Epstein-Barr virus subset chronic fatigue syndrome: thirty-six months follow-up. In Vivo. 2007 Sep-Oct;21(5):707-13.

Watt T, et al. Response to valganciclovir in chronic fatigue syndrome patients with human herpesvirus 6 and Epstein-Barr virus IgG antibody titers. J Med Virol. 2012 Dec;84(12):1967-74.

Montoya JG, et al. Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome. J Med Virol. 2013 Dec;85(12):2101-9.

Laub Biochem Specialty Labs, 2001-2002, research conducted by contract for Virology Branch of the Antiviral Research and Antimicrobial Chemistry Program (Dr. Christopher Tseng, Program Officer), Division of Microbiology and Infectious Diseases (DMID) Screening and Testing Program for Antiviral, Immunomodulatory, Antitumor and/or Drug Delivery Activities, National Institutes of Allergy and

What About Those w/o Infectious Correlations?

- Investigate further
  - Heavy metals

    Shin SR & Han AL. Improved Chronic Fatigue Symptoms after Removal of Mercury in Patient with Increased Mercury Concentration in Hair Toxic Mineral Assay. Korean J Fam Med. 2012 Sep;33(5):320-5.

    Pacini S, et al. Could cadmium be responsible for some of the neurological signs and symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Med Hypotheses. 2012 Sep;79(3):403-7.

  - Mold

    Brewer JH, et al. Detection of Mycotoxins in Patients with Chronic Fatigue Syndrome. Toxins (Basel). 2013 Apr 11;5(4):605-17.

  - Other infections
  - Dysglycemia and adrenal dysfunction
    - Zarković M, et al. [Disorder of adrenal gland function in chronic fatigue syndrome]. [Article in Serbian]. Srp Arh Celok Lek. 2003 Sep-Oct;131(9-10):370-4.
  - Food allergies, sensitivities and intolerances

Still No Luck?

- Treat based upon patient symptom picture
  - Mitochondrial support
    - **Magnesium (300-600 mg)**

      Cox IM, et al. Red blood cell magnesium and chronic fatigue syndrome. Lancet. 1991 Mar 30;337(8744):757-60.

    - **Coenzyme Q10 (150-300 mg)**

      Maes M, et al. Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder. Neuro Endocrinol Lett. 2009;30(4):470-6.

    - **Lipid Replacement Therapy (1000-6000 mg)**

      Nicolson G, et al. Clinical Uses of Membrane Lipid Replacement Supplements in Restoring Membrane Function and Reducing Fatigue in Chronic Diseases and Cancer. DISCOVERIES 2016, Jan-Mar, 4(1): e54.

    - **Nicotinamide Adenine Dinucleotide (NADH) (10 mg)**

Mitochondrial Support Cont.

- **D-Ribose (5 grams tid)**

  Teitelbaum JE, et al. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. J Altern Complement Med. 2006 Nov;12(9):857-62.

- **L-carnitine/Acetyl-l-carnitine/Propionylcarnitine (1000-3000 mg)**

  Vermeulen RC & Scholte HR. Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. Psychosom Med. 2004 Mar-Apr;66(2):276-82.

  Malaguarnera M. Carnitine derivatives: clinical usefulness. Curr Opin Gastroenterol. 2012 Mar;28(2):166-76.

- **Alpha lipoic acid (300-600 mg)**

  Nicolson G. Mitochondrial dysfunction and chronic disease: treatment with natural supplements. Altern Ther Health Med. 2014 Winter;20 Suppl 1:18-25.

  Kaiser JD. A prospective, proof-of-concept investigation of KPAX002 in chronic fatigue syndrome. Int J Clin Exp Med 2015;8(7):11064-11074

What Else May Help?

- **EFA Support (3.6.9)**

  Behan PO, et al. Comparison of oral nicotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. Acta Neurol Scand. 1990 Sep;82(3):209-16.

  Warren G, et al. 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. Acta Neurol Scand. 1999 Feb;99(2):112-6.

- **Botanical support**

  - *Withania somnifera* (300-600 mg)

    Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med. 2012;34(3):255-62.

  - *Panax ginseng* (500-2000 mg)

    Kim HG, et al. Antifatigue effects of Panax ginseng C.A. Meyer: a randomised, double-blind, placebo-controlled trial. PLoS One 2013;8(4):e61271.

  - *Glycyrrhiza glabra* (up to 4 grams, limit glycyrrhizic acid to <300 mg)

    Baschetti R. Chronic fatigue syndrome and liquorice. N Z Med J. 1995 Apr 26;108(998):156-7.

Other Integrative Strategies to Consider

- HRT/BHRT
- IM/IV Therapies
- Physiotherapy
- Hydrotherapy
- Acupuncture
- Massage
- CST
- LDN
- Organic Germanium

Faloona G & Levine S. The use of organic Germanium in Chronic Epstein-Barr Virus Syndrome (CEBVS): An example of Interferon

Take Home Messages

- CFS/SEID is a multisystem, multifactorial condition, that when an open heart and scientific inquiry are utilized, patient outcomes dramatically improve.
- Diagnose first, then treat; don’t “shotgun” it.
- Consider naturopathic therapeutic order whenever drawing up treatment plans.
  - Avoid overwhelming.
- K.I.S.S.

Thank You!

"Whoa! *That* was a good one! Try it, Hobbs — just poke his brain right where my finger is."