



LDN and CFS and Fibromyalgia

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CFS Definition

- ▶ Clinically evaluated, unexplained, persistent, or relapsing chronic fatigue that is of new or definite onset (has not been lifelong): is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

(CDC Criteria)

CFS Definition

Concurrent occurrence of four or more of the following symptoms:

- ▶ Self-reported impairment in short term memory
- ▶ Sore throat
- ▶ Tender cervical or axillary lymph nodes
- ▶ Muscle pain
- ▶ Multi-joint pain without joint swelling or redness
- ▶ Headaches of a new type, pattern, or severity
- ▶ Unrefreshing sleep
- ▶ Postexertional malaise lasting more than twenty-four hours

(CDC Criteria)

Fibromyalgia Definition 1990 ACR

A history of widespread pain. The patient must be experiencing pain or achiness, steady or intermittent, for at least 3 months. At times, the pain must have been present:

- ▶ On both sides of the body
- ▶ Both above and below the waist
- ▶ Midbody-for example, in the neck, midchest, midback, or headache.
- ▶ Pain on at least eleven of the eighteen tender points

(CDC Criteria)

Definition Myalgic Encephalomyelitis

- ▶ Postexertional fatigue
- ▶ Neurological impairment—cognitive dysfunction, Pain or sleep disturbance
- ▶ Immune/gastrointestinal impairment-sore throat, tender lymph nodes, poor immunity, abdominal dysfunction, or food sensitivities
- ▶ Energy metabolism/transport impairments-orthostatic, palpitations, air hunger, low body temp, sweating episodes, temperature intolerance

Definition CFS/FM/ME

Problems with definition?

- ▶ These are research definitions and exclude the majority of people that suffer from these syndromes
- ▶ Doesn't address underlying cause
- ▶ Promotes treatments limited to simple symptomatic therapies
- ▶ Disincentive to determine underlying abnormalities

CFS/FM/ME

CFS, CFIDS, FMS, MCS, ME, and GWS are overlapping syndromes and have same underlying pathophysiology.

CFS/FM/ME

- ▶ Many unanswered questions
- ▶ Vicious cycle pathophysiology
- ▶ Poorly treated in the “standard medical care” given in the US.

However, they are very treatable conditions!

Specificity

- ▶ If the CDC criteria is met, the diagnosis of CFS carries a high specificity and is associated with numerous documented physiologic abnormalities

How to Quickly Diagnose

Unexplained fatigue that significantly interferes with functioning and is associated with any two of the following:

- ▶ Brain fog
- ▶ Unrestful sleep
- ▶ Diffuse achiness
- ▶ Bowel dysfunction
- ▶ Unexplained neuropathy
- ▶ Recurrent and/or persistent infections or flu-like feelings
- ▶ Post exertional malaise

Dysfunctions

- ▶ Immune dysfunction
- ▶ Disordered sleep
- ▶ Hormonal deficiencies (not picked up on standard blood tests)
- ▶ Nutritional deficiencies
- ▶ Infections
- ▶ Mitochondrial dysfunction
- ▶ Coagulation defect
- ▶ Gastrointestinal dysfunction

Associated Conditions

- ▶ Chronic Sinusitis
- ▶ Multiple Chemical Sensitivity (MCS)
- ▶ Sensitivity to medications
- ▶ Low body temperature
- ▶ Allergies
- ▶ Sensitivity to temperature or barometric changes
- ▶ Intolerance to alcohol
- ▶ Hypoglycemia
- ▶ Dizziness/vertigo
- ▶ Low blood pressure
- ▶ Low grade fevers
- ▶ Heart palpitations
- ▶ Frequent infections
- ▶ Irritable Bowel Syndrome
- ▶ Vulvadynia
- ▶ Headaches (migraine and tension)
- ▶ Depression

Associated Conditions

- ▶ Autoimmune diseases (lupus, RA)
- ▶ Restless Leg Syndrome
- ▶ Weight Gain
- ▶ Increased thirst
- ▶ Low body temp
- ▶ Insulin resistance
- ▶ Yeast overgrowth
- ▶ Carpal tunnel syndrome
- ▶ Painful or irregular menstrual periods
- ▶ Sleep disturbances
- ▶ Brain fog
- ▶ Shortness of breath
- ▶ Confusion with numbers, names, words etc.
- ▶ Mood swings
- ▶ Numbness or tingling

Impact of CFS/FM

- ▶ An epidemiological study conducted in Australia published in the *Medical Journal of Australia* investigated the impact of CFS on patients' lives and found that 43% of patients that met the criteria for CFS were disabled to a degree that they were unable to attend school or work

Prognosis with Standard Medical Treatment

- ▶ A 5 year study entitled, *Illness and Disability in Danish CFS Patients at Diagnosis and 5-year follow-up* concluded, “CFS patients exhibit severe, long-term functional impairment.
- ▶ *Substantial improvement is uncommon, less than 6%*

Prognosis with Standard Medical Treatment

- ▶ An American study in which 64% of patients reported a certain degree of improvement.
- ▶ Only 2% experienced a complete recovery, with 40% remaining unable to work.

Bombardier, C.H. and Buchwald, D.
'Outcome and prognosis of patients with
chronic fatigue and chronic fatigue
syndrome,' *Archives of Internal
Medicine* 1995;155:2105-10

Prognosis with Standard Medical Treatment

- ▶ Joyce et al published a review entitled *The Prognosis of Chronic Fatigue and Chronic Fatigue Syndrome: A Systematic Review*.
- ▶ This review of 26 studies found that adults who met the CDC criteria of CFS had a poor prognosis with less than 10% recovering and the majority do not improve over time with standard medical care.

Prognosis with Standard Medical Treatment

- ▶ Prospective study of 146 FM patients compared standard medical care to standard medical care plus cognitive behavioral therapy (CBT).
- ▶ Standard medical care for CFS/FM includes muscle relaxants, antidepressants, NSAIDs, passive stretching and graded exercise
- ▶ Study found only 12% of individuals improved with standard care.

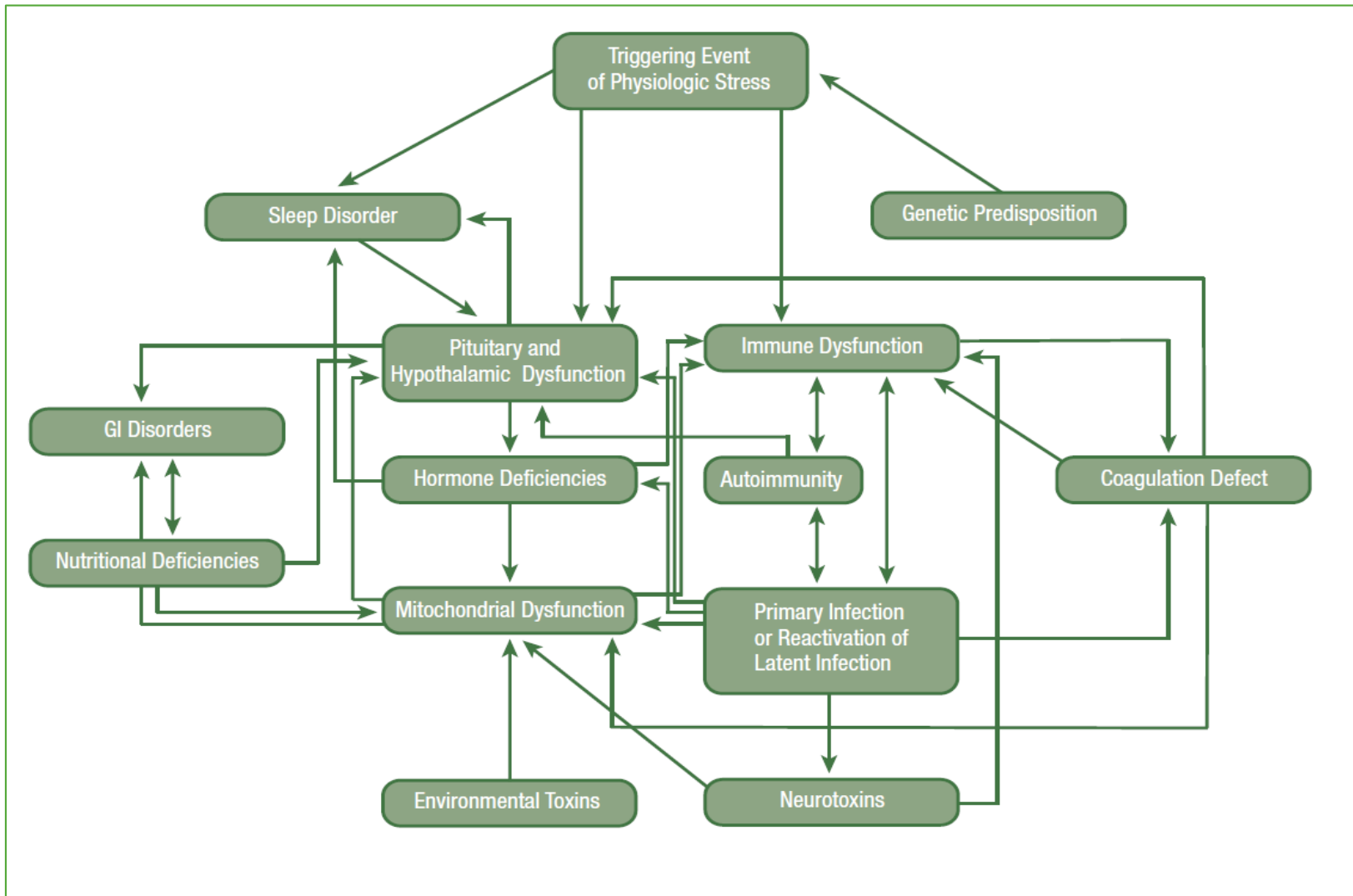
Why are these conditions so poorly treated?

- ▶ Typical medications used include antidepressants, NSAIDs, muscle relaxants and sleep meds.
- ▶ Only simple symptomatic treatments approved for FM that only help a very small percent of patients
- ▶ Many doctors don't believe it is a real condition-If they cannot treat it, it must not be real.
- ▶ Standard laboratory tests are usually normal (Can pick out CFS/FM on blood test about 80% of time and likely severity)
- ▶ Health insurers can avoid paying for treatment and testing if they can make believe these syndromes are not real or physical.
- ▶ 75 percent of those affected are female
- ▶ These conditions cannot be treated with the average eight minute office visit.

Pathophysiology of CFS/FM

- ▶ CFS/FM represent a mix of many different processes with a common endpoint
- ▶ Measurable hypothalamic, pituitary, immune and coagulation dysfunction.
- ▶ Each problem may trigger other problems

Cycle of Dysfunction



Chronic Fatigue Syndrome and Fibromyalgia
are very treatable Conditions!

When the multiple dysfunctions present are treated,
significant improvement is seen, almost without
exception.

Studies

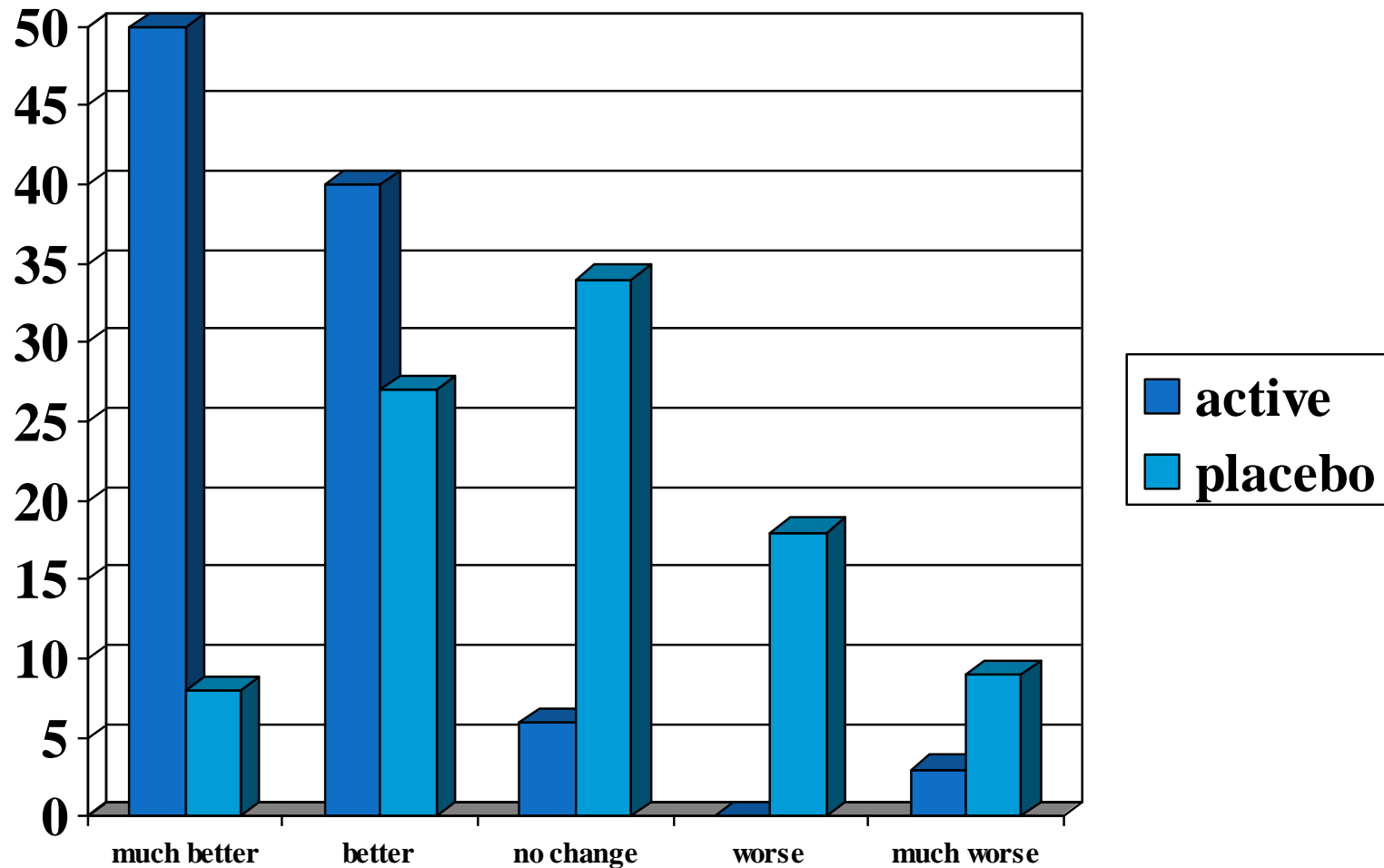
(Randomized double-blind, placebo control trial)

When the multiple dysfunctions are treated, including nutritional deficiencies, disorder sleep, hormonal deficiencies, infections and mitochondrial dysfunction, 57% of patients with CFS/FM will have complete resolution of symptoms and 39% will have incomplete but significant resolution of symptoms.

Summary: 96% will have significant improvement or total resolution of symptoms

Teitelbaum J, Bird B Greenfield R, et al. Effective Treatment of Chronic Fatigue Syndrome and Fibromyalgia-A Randomized, Double-Blind, Placebo-Controlled, Intent-To-Treat Study. J Chronic Fatigue Syndrome 2001;8(2):3-28

Journal of Chronic Fatigue Syndrome 2001



Outcomes Published in JCFS

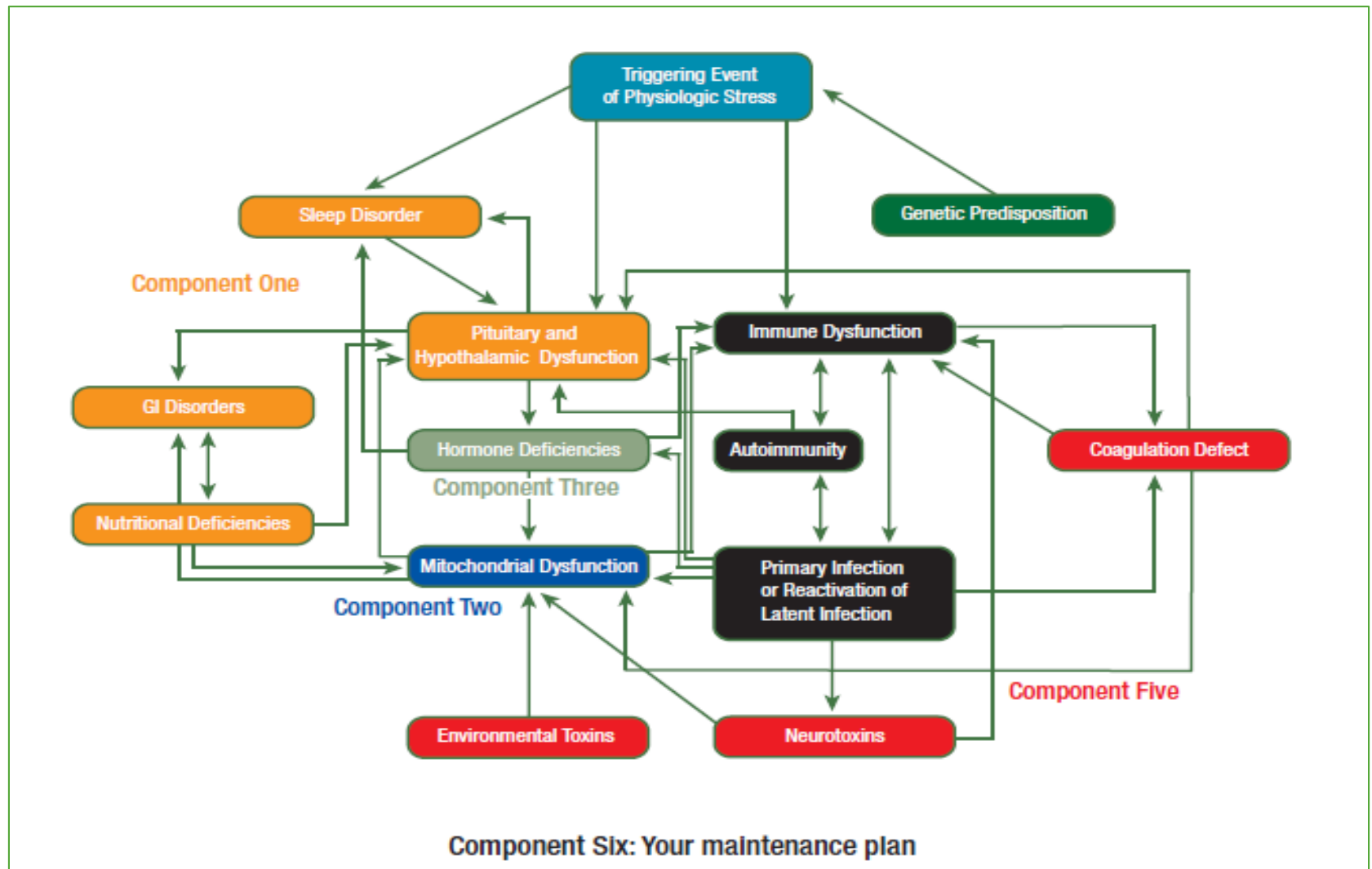
- ▶ 500 consecutive patients on computerized outcome assessment demonstrated that a multi-system treatment protocol that addresses the known physiologic abnormalities in CFS and fibromyalgia resulted in:
 - ▶ 94 percent of patients having overall improvement by the 4th visit
 - ▶ 75 percent noting significant overall improvement
 - ▶ 62 percent reported substantial overall improvement.
 - ▶ The average energy level and sense of well-being for patients doubled by the fourth visit.
- ▶ The effectiveness of this multi-system treatment was further confirmed through the analysis of the cumulative findings of over 40 independent physicians and over 5,000 patients.
- ▶ Prior to treatment at the Holtorf Medical Group, the patients had seen an average of 7.2 different physicians for the treatment of CFS and/or FM without significant improvement.

Holtorf, K. Diagnosis and Treatment of Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction in Patients with Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM). J of CFS 2008;14(3):1-14

Six Component Approach

- ▶ Component One Stabilize the Patient
- ▶ Component Two Mitochondrial Enhancement
- ▶ Component Three Balance the Hormones
- ▶ Component Four Treat the Infectious/Immune Components
- ▶ Component Five Addressing Unique Etiologies
- ▶ Component Six Maintenance

Integrated Approach to the Cycle of Dysfunction



Component 4



Treat the immune dysfunction
and Infectious component

Component 4

- ▶ TH1 to TH2 imbalance leads to vicious cycle of chronic infections
- ▶ Becomes “chicken and the egg”
- ▶ Thus, immune modulatory treatment is a key to the ability to successful treatment of chronic infections and overall successful treatment of CFS/FM

Viral

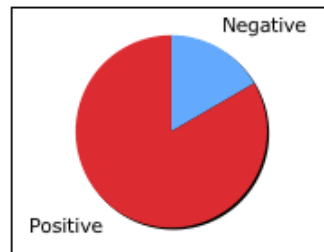
- ▶ Many possible
- ▶ EBV, HHV-6, CMV, enterovirus
- ▶ Did symptoms start with Mono and never fully recovered?
- ▶ Recurrent viral syndrome

HHV-6 and CFS/FM

- ▶ 70% of CFS/FM patients positive for HHV-6 using primary cell cultures and confirmation assays of monoclonal antibodies and PCR

HHV-6 and CFS/FM

Differentiated between active and latent virus



N= 12
 Positive = 10 (83%)
 Negative = 2 (17%)

83% of the studies demonstrate a large portion of CFS/FM patients have an active HHV-6 infection.

Assays that differentiated between active and latent virus: 83% positive

Author	Year	CFS +	Controls +	Method used	Result	Size of study
Nicolson	2003	31%	9%	PCR on serum or plasma	Positive	200 CFS, 100 controls
Koelle	2002	0%	0%	PCR on serum or plasma	Negative	22 CFS, 22 controls (twins)
Ablashi	2000	54%	8%	IgM Early Antigen antibodies	Positive	35 CFS , 25 controls
Ablashi	2000	+++	+	Lymphocyte response	Positive	10 CFS. 6 controls
Ablashi	2000	57%	16%	IgM Early Antigen antibodies	Positive	35 CFS, 25 controls
Reeves	2000	0%	0%	Viral isolation	Negative	26 CFS , 52 controls
Zorzenon	1996	73%	0%	CPE/IFA Positive	Positive	52 CFS, 51 controls
Wagner	1996	39%	-	Primary culture/isolation	Positive	107 CFS
Patnaik	1995	77%	12%	IgM Early Antigen antibodies	Positive	119 CFS , 165 controls
Secchiero	1995	3%	0%	PCR on serum or plasma	Positive*	39 patients, 37 controls
Buchwald	1992	70%	20%	Primary cell culture	Positive	113 CFS, 40 controls
Josephs	1991	43%	0%	Short term culture	Positive	7 CFS, 2 controls

Mycoplasma and CFS/FM

- ▶ 68% of CFS/FM patients were positive for Mycoplasma by PCR
- ▶ 63% of patients had active Mycoplasma vs. 9% controls with 50% having *M. fermentans* vs. 0% of controls

Infections and CFS/FM

- ▶ 52% of CFS/FM patients were positive for Mycoplasma, 31% positive for HHV-6 and 7.5% positive for CP vs. 6%, 9% and 1% of normals respectively

Lyme disease

- ▶ CDC estimates that the yearly reported cases are 10 fold what was previously thought (300,000 new cases/year up from 30,000), which is more prevalent than breast cancer and HIV combined
- ▶ Standard testing IFA with reflex to WB misses 40-90% of cases.
- ▶ Exploding likely secondary to multiple modes of transmission, including tics, mosquitoes, fleas, sexually transmitted

Lyme disease

- ▶ Patients with chronic Lyme are severely ill with a multisystem illness, with dysregulation and possibly damage to nearly every organ system
- ▶ Antibiotics alone unlikely to successfully treat
- ▶ RESULT- more and more patients are seeking CAM physicians to treat their CFIDS-like illness
- ▶ The longer one is ill with Lyme, the more difficult to treat
- ▶ Use Advanced Lab Lyme culture/IGeneX

Lyme disease

- ▶ When to expect Lyme
 - ▶ The more severe the CFS/FM
 - ▶ The more neurologic/autonomic symptoms/brain fog
 - ▶ The more “strange” symptoms the more likely Lyme disease

Markers of Immune Dysfunction

(Quest/Advanced Labs)

- ▶ Low NK cell function <30
- ▶ Low immune cell function (ATP production)
- ▶ low CD 57 (Labcorp)
- ▶ Elevated C4a
- ▶ VEGF
- ▶ Eosinophil cationic protein
- ▶ ACE above 30
- ▶ Immune activation of coagulation (D-dimer, soluble fibrin monomer, prothrombin fragment 1+2, thrombin antithrombin complex, PAI-1)
- ▶ Low IgG subclasses

NK Cell

- ▶ Low NK cell activity is an objective marker for severe disabling CFS
- ▶ A decrease in the CD57 is a marker for chronic Lyme disease and significant neurologic disease.

Ojo-Amaize EA, Conley EJ, Peter JB. Decreased natural killer cell activity is associated with severity of chronic fatigue immune dysfunction syndrome. *Clin Infect Dis*. 1994 Jan;18 Suppl 1:S157-9.

Clin Infect Dis 1994
Stricker RB, Winger EE. Decreased CD57 lymphocyte subset in patients with chronic Lyme disease. *Immunol Lett*. 2001 Feb 1;76(1):43-8.

Coagulation Defect

- ▶ Studies have found that 60-90% of CFS, FM and GWS patients have abnormal activation of the clotting system.

Blood Coagulation and Fibrinolysis, 1999
Blood Coagulation and Fibrinolysis, 2000
American Association of Clinical Chemistry,
2003

Immune modulation

- ▶ Increase TH1 and decrease TH2
- ▶ Boosting NK cell and lowering inflammatory cytokines
 - ▶ LDN
 - ▶ Thymosin alpha-1
 - ▶ GG 0.3- 1 gram IM/IV 3 grms and up
 - ▶ Ozone/UVBI
 - ▶ LDA/LDI (allergy elimination) *gluten
 - ▶ Regenapep
 - ▶ Antivirals
 - ▶ Antibiotics
 - ▶ Transfer factors
 - ▶ Mushroom extracts
 - ▶ Isoprinosine
 - ▶ High dose B12
 - ▶ GcMAF
 - ▶ Leukine/Neupogen
 - ▶ Heparin

LDN and FM

- ▶ Pilot study (12 FM patients, placebo-controlled, single blind, crossover design)
- ▶ Daily self-reported symptoms: baseline (2 weeks), placebo (2 weeks), LDN (8 weeks)
- ▶ Primary outcome of self-reported overall FM symptom severity, secondary symptom severity and mechanical pain testing q 2 weeks
- ▶ LDN reduced FM symptoms of FM by 30%
- ▶ Elevated ESR predicted response

Younger J, Mackey S. Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A Pilot Study. *Pain Med.* 2009 ; 10(4): 663–672.

LDN and FM

- ▶ Thirty-two FM patients, randomized, double-blind, placebo-controlled, crossover study
- ▶ Daily self-reported symptoms: baseline (2 weeks), placebo 4 weeks or LDN 12 weeks and 4 week f/u
- ▶ Primary outcome of self-reported overall FM symptom severity, secondary symptom severity and mechanical pain testing q 2 weeks.
- ▶ LDN reduced FM symptoms of FM by 28.8% vs. 18% with placebo
- ▶ LDN also associated with improved satisfaction with life and improved mood
- ▶ 32% met criteria for response (defined as a significant reduction in pain plus a significant reduction in either fatigue or sleep)

Younger J, Noor N, McCue R, Mackey S. Low-Dose Naltrexone for the Treatment of Fibromyalgia. *Arthritis & Rheum* 2013;65(2):529-538.



Thank You

Questions?