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EFFECTIVE TREATMENT OF CHRONIC FATIGUE SYNDROME

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OVERVIEW

Chronic fatigue syndrome (CFS) and its often simultaneously present cousin, fibromyalgia syndrome (FMS), are common names for an overlapping spectrum of disabling syndromes. It is estimated that FMS alone affects three to six million Americans, causing more disability than rheumatoid arthritis, and later research suggests a prevalence of CFS/FMS and/or disabling fatigue ranging from 7.3% to 12.9% across different countries.[1,2] The majority of patients I see in clinical practice who have FMS also have CFS.[3] Myofascial pain syndrome (MPS), pain caused by a localized area of muscle shortening, often shares many of the same underlying metabolic processes as FMS[4] and affects many millions more.[5] Structural abnormalities are more of a concern in MPS; however, because this article discusses the metabolic problems often seen in all three processes, I will often refer to the three (CFS/FMS/MPS) together.

Fortunately, two studies (including a recent randomized, controlled trial) done in our research center showed an average 90% improvement rate when using the "SHIN." protocol.[3,6] SHIN stands for Sleep, Hormonal support, Infections/Immune dysfunction, and Nutritional support. When a patient has fatigue and insomnia coupled with widespread pain, he or she is seen as having a body-wide "energy crisis." Treatment with the SHIN approach will help them. A recent editorial in the *Journal of the American Academy of Pain Management* noted that our studies, as well as years of clinical success, have confirmed that subclinical abnormalities are important, and that our comprehensive and aggressive metabolic approach to treatment is a powerfully effective part of the standard of practice for treatment of FMS and MPS patients.[7] Fortunately, although we still have much to learn, effective treatment is now available for the large majority of patients with these syndromes.[3,6]

Hypothalamic dysfunction has been implicated as a common denominator in these syndromes.[8,9] This may occur secondarily to mitochondrial dysfunction. Deficiencies of key mitochondrial metabolites such as Carnitine have been documented on muscle biopsy studies,[10,11] and improvement of fatigue states with mitochondrial-support treatment (eg, coenzyme Q_{10}, D-Ribose, Mg-K aspartate, NADH, magnesium, acetyl-L-carnitine) has been reported. Dysfunction of hormonal, sleep, and autonomic control (all centered in the hypothalamus) and energy-production centers can explain the large number of symptoms and why most patients have a similar set of complaints. To make it easier to explain to patients, we use the model of a circuit breaker in a house:

> *If the energy demands on your body are more than it can meet, your body "blows a fuse." The ensuing fatigue forces you to use less energy, protecting you from harm. On the other hand, although a circuit breaker may protect the circuitry in the home, it does little good if you do not know how to turn it back on, or that it even exists.*

This analogy actually reflects what occurs. Research in genetic mitochondrial diseases shows not simply myopathic changes, but also marked hypothalamic disruption. As energy stores are depleted, hypothalamic dysfunction occurs early on, resulting in the disordered sleep, autonomic dysfunction, low body temperatures, and hormonal dysfunctions commonly seen in these syndromes. In addition, inadequate energy stores in a muscle result in muscle shortening (such as in rigor mortis) and pain, which is further accentuated by the loss of deep sleep. Therefore, restoring adequate energy production and eliminating stresses that overutilize energy (eg, infections, situational stresses) restores function in the hypothalamic "circuit breaker" and also allows muscles to release, allowing pain to resolve. Our placebo-controlled study showed that when this is done, 91% of patients improved (vs 36% in the placebo group), with an average 90% improvement in quality of life compared to a 36% improvement in the placebo group. In addition, the majority of patients no longer qualified as having FMS by the end of 3 months.[3]

DIAGNOSIS

The criteria for diagnosing CFS, FMS, and MPS are readily available elsewhere. MPS is diagnosed by the presence of trigger points and taut bands. In my experience, there is a simple approach to diagnosing CFS and FMS that is very effective clinically. If the patient has the paradox of severe fatigue combined with insomnia, does not have severe primary depression, and these symptoms do not go away with vacation, the person likely has a CFS-related process. If there is also widespread pain, FMS is probably present as well. Both CFS and FMS respond well to proper treatment, as will be discussed.

Inadequate energy production (as is seen in mitochondrial myopathies) and energy needs greater than the body's production ability (as in "Female Athlete Triad" or some viral infections) have been shown to trigger hypothalamic dysfunction. I suspect that the same occurs in many other "energy stressors," such as infections and inflammation, disrupted sleep, pregnancy, hormonal and nutritional deficiencies, toxin exposures, and other physical and/or situational stresses.

Treatment

As mentioned earlier, using the SHIN acronym will facilitate the effective treatment of CFS (Figure 1). Let's begin with "S" for sleep.

S—Disordered Sleep

A foundation of CFS/FMS is sleep disorder. Using medications that increase deep restorative sleep so that the patient gets 7-9 hours of solid sleep without waking or hangover is critical. Start treatment with natural therapies or with a low dose of sleep medications that do not decrease stage 3-4 sleep. Continue to adjust the treatments each night until the patient is sleeping 8 hours a night without a hangover.

Due to next-day sedation and each medication having its own independent half-life, CFS/FMS patients respond better to a combination of low doses of several medications than to a high dose of one. The natural remedies I recommend starting with include the following:

1. Herbal preparations containing a mix of valerian root, wild lettuce, Jamaican Dogwood, passionflower, hops, and theanine. These 6 herbs can help reduce muscle pain, increase libido, and improve sleep.[12-16]
2. Melatonin: ½ –1 mg at bedtime.
3. 5-HTP (5 Hydroxytryptophan): 200-400 mg at night.
4. Calcium and magnesium at bedtime to promote sleep.

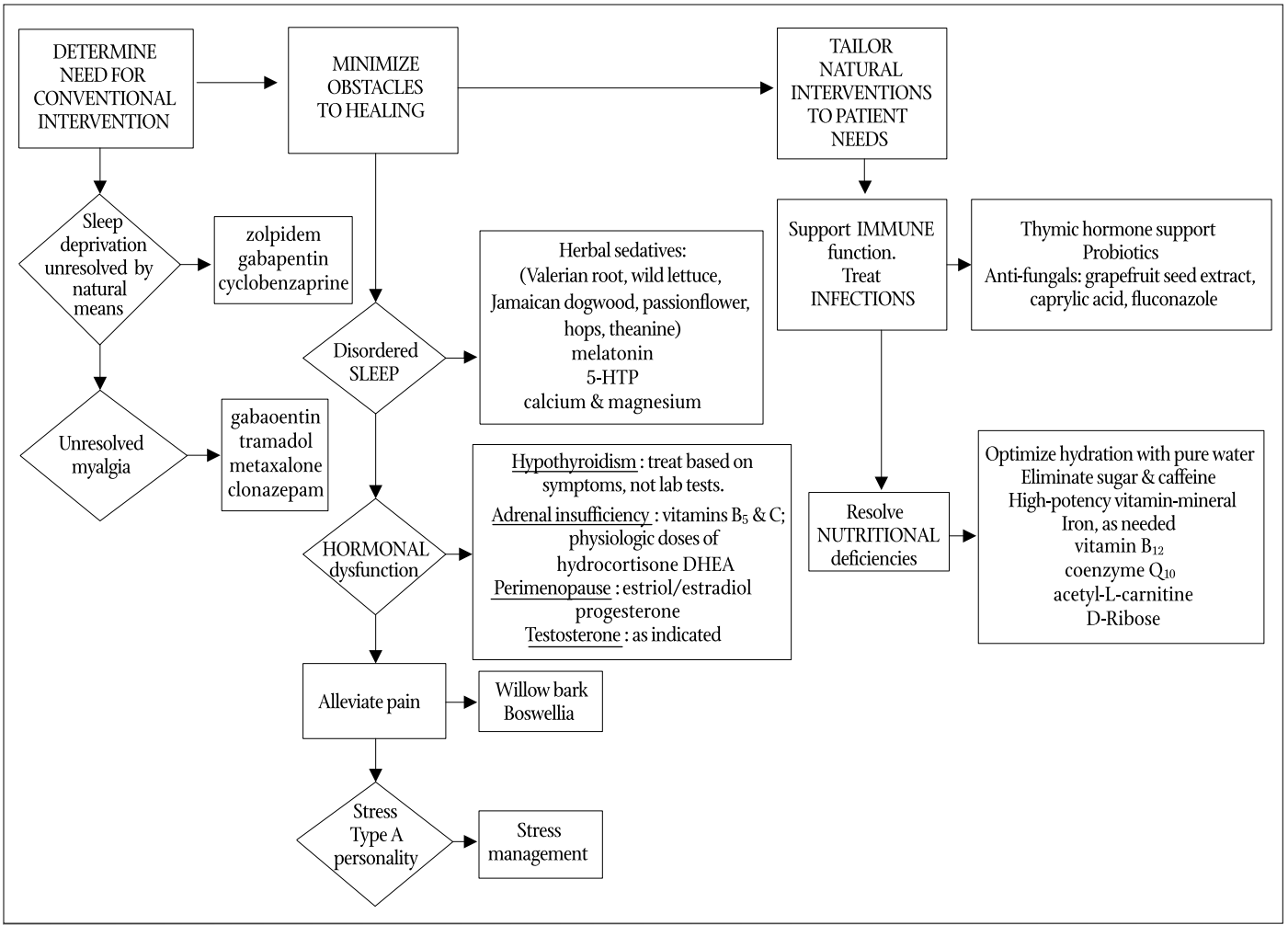

Figure 1
Effective Treatment of Chronic Fatigue Syndrome

If natural remedies do not result in at least 8 hours a night of sleep, consider these medications:

- zolpidem: 5-20 mg each night at bedtime.
- gabapentin: 100-900 mg at bedtime for sleep and pain, as well as restless leg syndrome (RLS).
- cyclobenzaprine: 10 mg, clonazepam – 5 mg, and/or carisprodol – 350 mg (use one of these first if myalgias are a major problem).
- trazodone: 50 mg (use ½ to 6 tablets each night at bedtime).

Some patients will sleep well with natural therapies and/or synthetic ones. Others will require a surprisingly large amount of sleep support because the malfunctioning hypothalamus controls sleep.

Although less common, three other sleep disturbances must be considered and, if present, treated. These are sleep apnea, upper airway resistance syndrome (UARS), and RLS, which is also fairly common in fibromyalgia.[17]

H—Evaluation and Treatment of Associated Hormonal Dysfunction

Hormonal imbalances are associated with FMS. Sources of imbalance include hypothalamic dysfunction, adrenal exhaustion from chronic stress, environmental toxins, and autoimmune processes, such as Hashimoto's Thyroiditis.

It is important to understand the limitations of testing and the normal ranges. Many blood tests use two standard deviations to define blood-test norms. By definition, only the lowest or highest 2.5% of the population is in the abnormal (treatment) range. This does not work well if more than 2.5% of the population has a problem. For example, it is estimated that as many as 20% of women over 60 years of age have hypothyroidsim.[18] Other labs, especially functional medicine labs, use normal ranges that are based on "medical decision points" (MDPs). These MDPs are based on where the literature suggests problems can occur. An example of this is the lowering of the upper limit for thyroid stimulating hormone (TSH) to 3.0 mIU/L by the American Academy of Clinical Endocrinology.[19] Nonetheless, it is important to treat the patient and not only the blood test. A level that may be healthy for many patients can represent a deficiency for others.

Thyroid Function

Suboptimal thyroid function is very common, and I find it reasonable to treat *all* chronic myalgia patients with thyroid-hormone replacement if their free T_4 blood levels are below even 50% of normal. Many CFS/FMS patients also have difficulty in converting T_4, which is fairly inactive, to T_3, the active hormone. Additionally, T_3 receptor resistance may be present, requiring higher levels.[20,21] In most CFS/FMS patients, I give an empirical trial of a Thyroid glandular supplement, ½ to 3 grains every morning, adjusted to the dose that feels best to the patient, as long as the free T_4 is not above the upper limit of normal. Many other alternatives, such as compounded combinations of T_4 and T_3, are also reasonable.

TSH testing is not reliable since hypothalamic dysfunction with hypothyroidism (based on symptoms and response to thyroid hormone) is common in fibromyalgia[22], and in hypothalamic hypothyroidism, the patient's TSH can be low, normal, or high.[23] The inadequacy of thyroid testing is further suggested by studies that show:

- most patients with suspected thyroid problems have normal blood studies.[24,25]
- when patients with symptoms of hypothyroidism and normal labs were treated with a thyroid supplement, a large majority improved significantly.[24]

In addition, remember that thyroid supplementation can increase a patient's cortisol metabolism and unmask a case of subclinical adrenal insufficiency. If the patient feels worse on low-dose thyroid replacement, he or she may need adrenal support as well.

Adrenal Insufficiency

The hypothalamic-pituitary-adrenal (HPA) axis does not function well in CFS/FMS.[8,26,27] Because early researchers were not aware of physiological doses of cortisol, they treated with high doses and their patients developed severe complications. William Jefferies, MD, author of *Safe Uses of Cortisol*,[28] helped us to understand the difference between physiological and pharmacological dosing. He found, in his experience with thousands of patients and years of use, that adrenal suppression and significant toxicity (besides gastrointestinal upset, weight gain, and fluid retention) were very uncommon with physiological dosing of hydrocortisone (ie, up to 20 mg a day).[28,29] Twenty mg of hydrocortisone is approximately equivalent in potency to 4-5 mg of prednisone.

Our study did not show adrenal suppression using lower hydrocortisone dosing.[3] Dr Jefferies, with thousands of patient-years' experience in using low-dose hydrocortisone, recommends an empirical trial of 20 mg a day of hydrocortisone for all patients with severe, unexplained fatigue, and has found this to be quite safe for long-term use.[28,29] Confirming this, our research and clinical experience suggest that using hydrocortisone at 20 mg a day or less in CFS and FMS patients is safe and often helpful. Although this has not been subjected to controlled research, clinically, many patients find it to be extremely helpful.

Symptoms of an underactive adrenal gland include hypoglycemia/irritability when hungry, weakness,

hypotension, dizziness, and recurrent infections—all of which are common in CFS/FMS. Although a baseline morning cortisol of >6 mcg/dl is often considered "normal," most healthy people run approximately 16-22 mcg/dl at 8:00 AM.

My treatment guidelines are that if the baseline cortisol is less than 16 mcg/dl, or if the patient's symptoms suggest inadequate adrenal function, I treat with a therapeutic trial of 5-15 mg hydrocortisone in the morning, 2.5-10 mg at lunchtime, and 0-2.5 mg at 4:00 PM (maximum of 20 mg a day). After 9-18 months, the patient can often taper off the hydrocortisone. Remember, more is not better.[30]

In addition to supplying very low-dose cortisone, it is important to supply nutritional support for the adrenal, as well as teaching the patient mind-body approaches that can decrease worry and increase relaxation, thus taking stress off the adrenals. I teach my patients to ask themselves this simple question when they start getting worried or stressed out: "Am I in imminent danger?" The answer is almost always "no," which seems to help patients to "stand down" from their "fight or flight" reaction. Nutritional support should include vitamin C and pantothenic acid, as well as adrenal glandulars. Herbals such as ginseng and licorice can also be helpful.

DHEA

Dehydroepiandrosterone (DHEA) is a major adrenal hormone that has recently been getting a lot of attention in the press for its role as a "fountain of youth" hormone.[31] DHEA is stored as DHEA-sulfate (DHEA-S), and levels of the activated free DHEA fluctuate throughout the day. Because of this, I recommend checking serum DHEA-S levels rather than DHEA levels.

Many CFS/FMS patients have suboptimal DHEA-S levels, and the benefit of treatment is often dramatic. Most women need 5-25 mg per day, and most men need 25-50 mg per day. I use the middle of normal range for a 29-year old, keeping the DHEA-S level at 150-180 mcg/dl in women, and at 350-480 mcg/dl in men. Although DHEA and testosterone levels normally drop with age, many practitioners feel this is not necessarily healthy. For example, studies show that low testosterone and low DHEA may be associated with insulin resistance and glucose intolerance.[32-34]

Low Estrogen and Testosterone

Although we are trained to diagnose menopause by symptoms such as cessation of periods, hot flashes, and elevated follicle-stimulating hormone (FSH) and leutenizing hormone (LH) levels, these are late symptoms. Estrogen deficiency often begins many years before, and may coincide with the onset of CFS/FMS.[35]

The initial symptoms of estrogen deficiency are poor sleep, poor libido, brain fog, achiness and, especially, worsening of CFS/FMS symptoms in the days to a week before the period. I prefer to have the pharmacist make a combination of estriol and estradiol (Bi-Est) 2.5 mg plus progesterone 30-50 mg plus testosterone 4 mg—all in 1/10 or 2/10 of a CC of cream (which can be applied to the mucosal surface of the labia each evening).

Testosterone Deficiency

Among my CFS/FMS patients, 70% of men and many women have free testosterone levels in the lowest quartile, while their total testosterone levels are normal. I therefore recommend blood testing for "free testosterone." A recently completed study (not yet published) found that treating low testosterone in women decreases FMS pain. As noted above, supplementation can be done easily by adding 4 mg of testosterone to the estrogen cream. Testosterone supplementation also decreases sex hormone-binding globulin (SHBG), thus making more free hormone available.

Testosterone supplementation can also cause elevated thyroid hormone levels in men taking thyroid supplements. In addition, despite the concerns about athletes using very high levels of *synthetic* testosterone, it is important to remember that research shows that raising a low testosterone level in men using *natural* testosterone actually results in lower cholesterol, decreased angina and depression, and improved diabetes.[34]

I—Immune Dysfunction and Infections

Immune dysfunction is part of the process for CFS/FMS patients. Opportunistic infections present in CFS/FMS include yeast/Candida, chronic upper respiratory infections (URIs) and sinusitis, bowel infections, and chronic, low-grade prostatitis, all of which need to be treated.

Chronic sinusitis responds poorly to antibiotics, but responds well to antifungals.[36] Bowel infections with alterations of normal bacterial flora, fungal overgrowth, and parasitic infections are also frequently present, as is reflected by the patient's bowel symptoms. Because of the lack of a definitive test for yeast overgrowth, there is little research published in this area, and treatment is controversial; it is empirical and based on the patient's history. Yeast vaginitis, onchomycosis, sinusitis, a history of frequent antibiotic use (such as tetracycline for acne), *or* gas, bloating, diarrhea, or constipation warrant an empirical, therapeutic antifungal trial. Many CFS/FMS patients who have not responded to other therapies for spastic colon or sinusitis have responded dramatically to anti-fungal treatments. I give an empirical trial of antifungal therapy in most CFS/FMS/MPS patients. I treat with sugar avoidance, a mix of anti-fungal herbs (eg, grapefruit seed extract and caprylic acid), and acidophilus for 5 months. After 4 weeks on the herbs and acidophillus, I add 200 mg daily of fluconazole for 6 weeks.

Parasitic, occult infections such as chlamydia,

Mycoplasma incognitus, human herpesvirus 6, cytomegalovirus, and Epstein-Barr virus are also sometimes active in CFS/FMS patients. In these cases, I often use thymic hormone mimics, which are excellent immune stimulants for acute infections as well.

Restoring normal gut flora and eliminating bowel infections are a critical part of treatment for many reasons, including improving digestion and nutrition. This brings us to the "N," perhaps the most important part of the SHIN acronym of treatment.

N—Nutritional Deficiencies

CFS/FMS patients are often nutritionally deficient. In addition to bowel infections, which result in potential nutrient losses and increased needs secondary to illness, the "Standard American Diet" (SAD) is nutritionally inadequate. People often ask, "Which vitamin am I low in?" when they tend to be deficient in many nutrients. For example, B vitamins, magnesium, iron, D-Ribose, coenzyme Q_{10}, malic acid, glutathione, and carnitine are essential for mitochondrial function[11,37] and energy production. Inadequate energy production, for instance, can result in muscle shortening (think "rigor mortis") with associated pain, poor immune and liver (detoxification) function, cognitive dysfunction, etc. Optimal nutrient support is also critical for many other processes. Although blood testing is not reliable or necessary for most nutrients, I do recommend that B_{12}, Fe (iron), total iron-binding capacity, and ferritin levels be checked. I begin CFS/FMS patients on the following nutritional regimen:

1. A *quality multivitamin suited for their needs*. It should contain at least a 50 mg B-complex, 150 mg of magnesium (as the glycinate), 900 mg of malic acid, 600 IU of vitamin D, 500 mg of vitamin C, 15 mg of zinc, 200 mcg of selenium, 200 mcg of chromium, and amino acids. Because there are dozens of important nutrients and patients got tired of taking handfuls of tablets, I now use a powdered multivitamin so that 1 capsule plus a single drink replaces more than 35 tablets or capsules of supplements each day. This should be taken long-term.
2. *Supplement with iron* if the iron percent saturation is under 22% or the ferritin is under 40 mg/ml. Iron should be taken on an empty stomach and at least 6 hours away from thyroid hormones.
3. If the B_{12} level is under 540 pg/ml, I recommend *B_{12} injections*, 3,000 micrograms intramuscularly 3 times a week times for 15 weeks, then as needed based on the patient's clinical response.[38-41]
4. *Coenzyme Q_{10}*: 100–200 mg a day.
5. *Acetyl-L-carnitine*: 500 mg twice daily for 4 months.
6. *D-Ribose*: 1 scoop 3 times daily for 3 weeks, then twice daily.
7. The patient should *avoid sugar and caffeine*, and *water intake should be increased* as well. Most patients find that a *high-protein, "whole foods" diet* feels best, but it is important to remember that there is a broad range of biological individuality, so I encourage patients to "check in with their bodies" a few hours after eating to see what foods help them to feel the best.

General Pain Relief

Although many kinds of pain will often resolve within three months of simply using the SHIN treatment as discussed above, it is also critical to eliminate pain directly. Several studies show a marked analgesic and anti-inflammatory effect from adequate doses of two herbals: willow bark (containing at least 240 mg of salicin) and boswellia (900+ mg). Willow, for example, has been shown to be as effective as Motrin and Vioxx.[42,43] These herbals are excellent for arthritic, inflammatory, and other pains. The herbs discussed earlier (under "Sleep)" can also help muscle pain. Clinically, gabapentin, tramadol, and metaxalone are also far more effective for CFS/FMS/MPS pain than nonsteroidal anti-imflammatory drugs (NSAIDs).

Psychological Well-being

Many illnesses are associated with various psychological profiles. In CFS/FMS, a common profile is a "mega-type-A" over-achiever who, because of low self-esteem in childhood, overachieves to get approval. They tend to be perfectionists and have difficulties protecting their boundaries—that is, they say *yes* to requests when they feel like saying *no*. Instead of responding to their bodies' signals of fatigue by resting, they redouble their efforts. Taking time to rest and getting and staying out of abusive personal and work environments is critical to psychological well-being. A simple approach is to teach patients (and yourself) to only do and keep their attention on things that, from a centered place, feel good. Joseph Campbell put it beautifully and succinctly when he said, "Follow Your Bliss!"[44]

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I have a policy of not taking money from any natural or pharmaceutical companies, and 100% of the royalties for my products go to charity. I serve on the scientific advisory board of ITI/Enzymatic Therapy, but accept no compensation, honorariums, etc from them because of my conflict-of-interest policy.