A Confounding Condition

Treating chronic fatigue syndrome and Fibromyalgia requires addressing the underlying problems.

When it comes to treating patients with chronic fatigue syndrome (CFS) and fibromyalgia (FM), doctors are often at a loss. Because they can't figure out what's wrong, many consider CFS and FM “waste basket” diagnoses. Others simply dismiss the symptoms as psychiatric in nature.1-3

This certainly is a disservice to the estimated 4 percent to 7 percent of the population that suffers from these conditions. These disorders, which strike women four times as much as men,1-3 are consistently associated with a unique set of physiologic abnormalities.4-71 Physicians need to employ a multisystem approach, instead of resorting to single-drug modalities for each symptom.12,16,72-87 This comprehensive approach is largely becoming the standard of care and is effective in 80 percent of patients with these conditions.

What is Fibromyalgia?
To be diagnosed with FM, patients must experience pain for at least three months. They also must feel pain upon palpation at 11 out of 18 tender points.88 This criteria, however, is criticized for not taking into account the essential elements of FM, such as fatigue, sleep disturbance and cognitive dysfunction.89-93

For a CFS diagnosis, patients must experience fatigue that doesn't improve with bed rest. This fatigue should impair the average daily activity level by more than 50 percent for at least six months. People also must experience four or more of the following symptoms: cognitive dysfunction, sore throat, joint pain, muscle pain, headaches, nonrefreshing sleep and post-exertional malaise.94

The diagnostic criteria for FM and CFS are limited. Furthermore, there's no accepted

An overwhelming amount of peer-reviewed medical literature documents pituitary and hypothalamic dysfunction in CFS and FM patients.
laboratory marker to define these conditions. Consequently, physicians have difficulty properly diagnosing FM and CFS. But despite different modes of diagnosis (physical exam vs. history), CFS and FM share numerous common dysfunctions and coexist 50 percent to 70 percent of the time, depending on the study. Therefore, from a clinical standpoint, we will consider these illnesses together. The range of symptoms in these conditions includes fatigue, sleep disturbances, muscle pain, cognitive dysfunction, gastrointestinal dysfunction, headaches and post-exertional malaise.

Note that the unique physiologic hallmarks of CFS and FM don't exist in other fatiguing illnesses. These syndromes are complicated, involving pituitary and hypothalamic dysfunction, immune dysfunction, sleep stage disorder, mitochondrial dysfunction, hormonal deficiencies, coagulation defects and chronic infections.

In addition, each physiologic abnormality can cascade into other problems. For example, chronic stress can produce hypothalamic, pituitary and immune dysfunction—signature signs of fibromyalgia. Immune dysfunction can reactivate viral and intracellular bacterial infections. This can further suppress hypothalamic and pituitary function, causing mitochondrial dysfunction and coagulation dysregulation.

The hypothalamic and pituitary dysfunction produces hormonal deficiencies. In a vicious cycle, the chronic infections can further suppress mitochondrial function and produce global cellular dysfunction and a subsequent immune activation that causes a coagulation defect. This, in turn, worsens cellular function. This cascade produces multisystem illness that causes a broad range of often perplexing symptoms.

The Multisystem Approach
CFS and FM diagnoses often frustrate physicians because there’s no clear cause or treatment. Doctors typically treat the problem with NSAIDS, antidepresants and muscle relaxants. But these drugs are largely ineffective because they fail to address the underlying causes of the problem. In addition, they have a high incidence of significant side effects, including anxiety and insomnia. Muscle relaxants, too, can be addictive. Serotonin-norepinephrine reuptake inhibitors (SNRIs) and anticonvulsants may offer some benefit (Pregabalin is the first medication that is FDA approved to treat FM), but they’re often ineffective. In addition, the majority of patients don’t tolerate the medication well.108-110

Given these facts, physicians should take the following multisystem approach to address both diagnoses.

COMPONENT ONE: Stabilize the Patient
Physicians commonly address the pain and sleep disturbances of CFS and FM with medications. These drugs can help some patients, but the overwhelming majority needs further treatment. Sadly, this first stage of treatment is the only course many doctors prescribe.

COMPONENT TWO: Mitochondrial Enhancement
The mitochondria are the energy factories for the cells where sugar is burned and energy is produced in the form of adenosine-tri-phosphate (ATP). When the mitochondria are not working properly, the cells and tissues of the body are starved for energy. This abnormality may be the common endpoint for all the dysfunctions in CFS and FM.

Not only do the reduced amounts of metabolized glucose produce weight gain, reduced aerobic energy production requires the body to rely on anaerobic metabolism. This causes fatigue, muscle pain, poor concentration, gastrointestinal dysfunction, headaches and post-exertional malaise.

Mitochondria can be poisoned by numerous substances, including environmental toxins, pesticides, chronic bacterial, viral and fungal infections, neurotoxins and nutritional and hormone deficiencies. Mitochondria dysfunction has the greatest impact on the most active tissues, including the hypothalamus, pituitary, muscle, nerve and immune cells. These are the major dysfunctions of these conditions and can significantly explain the symptoms of CFS/FM. Supplying mitochondrial intermediates and nutrients, such as magnesium, carnitine, D-ribose, CoQ10 and glutathione, can improve mitochondrial function and alleviate symptoms of CFS and FM.111-116

COMPONENT THREE: Balance the Hormones
An overwhelming amount of peer-reviewed medical literature documents pituitary and hypothalamic dysfunction in CFS and FM patients. As a result, patients often have multiple hormonal deficiencies, including thyroid, growth hormone and cortisol. Physicians often miss these hormonal deficiencies because standard
blood tests lack sufficient sensitivity to detect such centrally mediated deficiencies. However, they need to pay close attention to the following hormones:

**Thyroid.** Numerous studies have demonstrated that central hypothyroidism as well as cellular resistance to thyroid hormone exists in the overwhelming majority of patients with FM and CFS. This persists, despite their having normal thyroid function tests (TFTs). For instance, a study published in the Journal of Rheumatology looked at the incidence of central hypothyroidism in patients with FM.6 Through thyrotropin releasing hormone (TRH) testing, all of the patients with FM had central hypothyroidism, despite having baseline TFTs in the normal range. More than 90 percent of the time, standard TSH and T4 testing misses central mediated hypothyroidism.117

Emerging evidence, however, shows free T3/reverse T3 (rT3) ratios can be a useful indicator of tissue thyroid levels. This may, in fact, help physicians assess tissue thyroid effect with central hypothyroidism and chronic physiologic stress.118-120 Instead of T4 normally converting intracellularly to the active T3 in peripheral tissue, T4 is preferentially converted to reverse T3. Therefore, increasing levels of rT3 and diminishing levels of T3 are indicators of low tissue thyroid effect. Free T3 and rT3 tests can be ordered at most major clinical laboratories. A free T3/rT3 ratio that's less than 2 pg/ng is consistent with low tissue thyroid activity.

Because T4 to T3 conversion in these conditions is diminished, it's not surprising that T4 supplementation has little effect, but that treatment with T3 is significantly effective.118-123 In a double-blinded, placebo-controlled trial by Lowe, et al., T3 therapy was safe and effective for treating euthyroid (TFTs in the normal range) FM. Patients reported a highly significant improvement in pain, fatigue, stiffness, headache, sleep disturbance, bowel disturbance, depression, cognitive dysfunction, anxiety, cold intolerance, paresthesias and exercise endurance. They noted no significant adverse effects, despite having TFTs that would normally indicate hyperthyroidism, with a suppressed TSH, low free T4 and high free T3 levels. No adverse effects were reported on heart, bone muscle and liver function, which were monitored every two months for eight months.121

In a small, double-blinded, placebo-controlled crossover study of four patients, T3 was administered and withdrawn in two T3 phases and two placebo phases over nine months.124 All patients had normal baseline TFTs. All significantly improved in the T3 phases and deteriorated during placebo phases. No adverse target tissue effects were seen and all patients chose to continue treatment after the study's end. This study did not demonstrate any adverse cardiac or bone effects.125

T3 is available as the brand Cytomel or as a compounded timed-release preparation, which has the advantage over Cytomel in minimizing serum fluctuations of T3. Optimal doses can vary significantly among patients and should be slowly titrated with careful monitoring for signs of excess, such as palpitations, rapid heart rate and anxiety.

**CFS and FM diagnoses often frustrate physicians** because there's no clear cause or treatment. Doctors typically treat the problem with NSAIDS, antidepressants and muscle relaxants.

**Cortisol.** Most patients with CFS and FM suffer from clinically significant adrenocortical dysfunction due to hypothalamic and pituitary dysfunction. The hypothalamic and pituitary function in these conditions (potentially due to mitochondrial function) results in inadequate cortisol production.

All studies that have used central acting stimulation testing in CFS and FM have shown significant hypothalamic-pituitary-adrenal (HPA) axis dysfunction.4 However, physicians often believe a normal serum cortisol level or ACTH stimulation test generally rules out significant HPA axis dysfunction. These tests are much more useful for primary hypoadrenalism. They, however, lack sufficient sensitivity to detect the central HPA axis dysfunction.4

The current evidence supports using physiologic doses of cortisol as an appropriate component of a multisystem treatment protocol for CFS and FM. Specialists should consider a therapeutic trial of cortisol in the majority of these patients, especially those with signs or symptoms consistent with adrenal dysfunction, low blood pressure and/or serum levels that are low or in the low-normal range.

Physiologic replacement of cortisol at doses of replacement can improve energy, strength, cardiac function, cognitive function, immunity and psychological well-being. It also decreases body fat, increases lean muscle and improves quality of life. It also significantly improves symptoms in these conditions with little or no side effects.2,21,124 Because of the pulsatile nature of growth hormone production and short half-life (20 to 50 minutes), routine serum growth hormone levels cannot be used to determine overall production. However, IGF-1 levels correlate with overall growth hormone production and are relatively stable in the serum. While a normal IGF-1 level doesn't rule out a significant growth hormone deficiency, the IGF-1 level is the best estimate of growth hormone production and effect. Low-normal IGF-1 levels are consistent with a relative growth hormone deficiency.

Titrating the dose of growth hormone to achieve IGF-1 levels in the upper limit of normal is safe, well tolerated and offers significant clinical benefits. Typical doses are 0.5-2 iu injected subcutaneously daily. Patients can start with a three-month therapeutic trial. We must monitor for water retention, which can produce joint pain and carpal tunnel syndrome. Insulin sensitivity may temporarily decline as well. Such treatment
Evidence also suggests that neurotoxins are a potential cause or contributing factor to CFS and FM symptoms. Visual contrast sensitivity testing and serum C3(a) and C4(a) can help us assess the potential for such exposure.

**COMPONENT FIVE:**
Address Unique Etiologies

Several cycles of dysfunction occur in these conditions that can produce unique pathological etiologies. For instance, chronic infections can cause an abnormal immune activation of coagulation. This produces a fibrin coating on the lumen of the vessel, causing impaired oxygen and nutrient transfer. Fatigue, muscle aches and cognitive dysfunction.2,57-62

If suspected, the diagnosis can be made by testing a coagulation panel of soluble fibrin monomer, thrombin-antithrombin complex, D-dimer and plasminogen activator-inhibitor-1.2,17-62 Heparin can help such patients.2,58

The Journal of Chronic Fatigue Syndrome recently reported our center's novel use of a computerized symptom assessment that evaluated the multisystem treatment protocol for more than 500 consecutive patients with CFS and FM.4

Ninety-four percent of patients had overall improvement by the fourth visit, with 75 percent noting significant overall improvement and 62 percent reporting substantial overall improvement. In subsequent visits, the majority of patients continued to improve. The average energy level more than doubled by the fourth visit, going from an average of 2.98 at baseline to 6.39, and then to 6.77 and 7.67 at the seventh and ninth visits, respectively.

The average sense of well-being more than doubled by the fourth visit, increasing from a baseline average of 3.03 then to 6.29, 7.45 and 6.83 on the fourth, seventh and ninth visit, respectively.

Subsequently, more than 40 physicians were trained to use a simplified treatment algorithm at 17 centers across the country. This multicenter study included more than 4,000 consecutive CFS and FM patients who were treated with this simplified algorithm and tracked via the same computerized patient assessment system. Eighty-five percent of patients improved by the fourth visit, with 56 percent and 40 percent reporting significant and substantial improvement by the fourth visit. By the seventh visit, 62 percent of patients reported significant improvement, and 46 percent indicated substantial improvement.8,7

By addressing the multiple physiologic abnormalities that occur with CFS and FM, we can give our patients hope for dealing with these debilitating disorders.

| KENT HOLTORF, MD, is an expert in treating chronic fatigue syndrome, fibromyalgia, complex endocrine dysfunction and chronic infections (including EBV, HHV6 and Lyme disease). Dr. Holtorf received his doctorate of medicine from St. Louis University with residency training at UCLA. He has personally trained numerous physicians across the country to effectively treat chronic fatigue syndrome, fibromyalgia and chronic infectious diseases. Additionally, Dr. Holtorf was the founding medical director and developed the protocols for Fibromyalgia and Fatigue Centers and other centers across the country. |

| Disclosure: Dr. Holtorf indicates that he has no affiliations with any commercial entities, directly or indirectly referenced in this article. |
References:
38. De Meirleir K et al. A 37 kDa 2-5A binding protein as a potential biochemical mark-


60. Harrison H, Ryser CA., Brewer J, Berg D. Procoagulant Genetic Factors in a Pooled Cohort of 582 Chronic Fatigue Syndrome, Fibromyalgia and Related Chronic Illness Cases. VIIth International Conference American Association for Chronic Fatigue Syndrome (AACFS), Oct, 2004, Madison, WI, USA.


myalgia and Other Related Illnesses. Fort Lauderdale, FL Jan 12-14, 2007.
86. Holtorf K, Wightman W, Tenenbaum S, Shah P, White MD. Outcome database of 5000+ CFS/FM patients. Dallas TX, Fort Worth TX, Las Vegas NV, Salt Lake City UT, Portland OR, Seattle WA, Atlanta GA, Norwalk CT, Boston MA, Philadelphia PA, Cleveland OH, Denver CO, Houston, TX, Detroit MI, Pittsburgh PA, Amarillo TX, Houston TX.
87. Holtorf K, Wightman W, Tenenbaum S, Shah P, White MD. Outcome database of 5000+ CFS/FM patients. Dallas TX, Fort Worth TX, Las Vegas NV, Salt Lake City UT, Portland OR, Seattle WA, Atlanta GA, Norwalk CT, Boston MA, Philadelphia PA, Cleveland OH, Denver CO, Houston, TX, Detroit MI, Pittsburgh PA, Amarillo TX, Houston TX.
93. Crofford LJ, Clauw DJ. Fibromyalgia: where are we a decade after the American College of Rheumatology classification criteria were developed? [editorial]. Arthritis Rheum 2002;46:1136–8.
women's health


117. Rose SR; Lustig RH; Pitukcheewanont P; Broome DC; Burghen GA; Li H; Hudson MM; Kun LE. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. J Clin Endocrinol Metab 1999;84(12):4472-9.


124. Lerner AM, Zervos M and Chang CH et al. A small, randomized, placebo-controlled


128. Montoya et al. Use of valganciclovir (Valcyte) in patients with elevated antibody titers against Human Herpesvirus-6 (HHV-6) and Epstein-Barr Virus (EBV) who were experiencing central nervous system dysfunction including long-standing fatigue. Journal of Clinical Virology 2006;37:S33-38.

