

# A Confounding Condition

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

**W**hen 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.<sup>1-3</sup>

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,<sup>1-3</sup> are consistently associated with a unique set of physiologic abnormalities.<sup>4-71</sup>

Physicians need to employ a multisystem approach, instead of resorting to single-drug modalities for each symptom.<sup>12,16,72-87</sup> 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.<sup>88</sup> This criteria, however, is criticized for not taking into account the essential elements of FM, such as fatigue, sleep disturbance and cognitive dysfunction.<sup>89-93</sup>

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.<sup>94</sup>

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



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**MANY PHYSICIANS** incorrectly feel that CFS and FM are merely “waste basket” diagnoses. They may also dismiss the symptoms as psychiatric in nature. However, overwhelming evidence shows that CFS and FM symptoms are consistently associated with a unique set of physiologic abnormalities that can be effectively treated.

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.<sup>4-71</sup> 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, antidepressants and muscle relaxants. But these drugs are largely ineffective because they fail to address the underlying causes of the problem.<sup>95-109</sup> In addition, they have a high incidence of significant side effects, including anxiety and insomnia.<sup>95,69</sup> 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.<sup>108-110</sup>

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 postexertional 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.<sup>111-116</sup>

### 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<sup>4-21</sup>, 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.<sup>4,5,6,7,17-21</sup> 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).<sup>6,11-16</sup>

For instance, a study published in the *Journal of Rheumatology* looked at the incidence of central hypothyroidism in patients with FM. 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.<sup>117</sup>

Emerging evidence, however, shows free T3/reverse T3 (rT3) ratios can be a useful indica-

effects were reported on heart, bone muscle and liver function, which were monitored every two months for eight months.<sup>121</sup>

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.<sup>118</sup> 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.<sup>123</sup>

T3 is available as the brand Cytomel or as a compounded timed-released 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.

5 mg to 15 mg a day are safe, with little or no associated risk. Such physiologic doses don't carry the risk of adrenal and immune suppression or bone loss, which are well known risks of pharmacological doses of corticosteroids. Cortisol treatment carries significantly less risk and a greater potential for benefit than standard treatments, such as anti-depressants, muscle relaxants, anticonvulsants and narcotics.<sup>4</sup>

**Growth Hormone.** Studies also show CFS and FM patients have diminished secretion of growth hormone secretion, a single-chain polypeptide produced in the pituitary gland with a wide range of metabolic and cellular effects. Growth hormone stimulates the production of insulin-like growth factor-1 (IGF-1) in the liver. Both play an important role in regulating body composition, lipid profiles, tissue repair, cardiac and neuronal functioning and bone mineral density. A great deal of peer-reviewed research, including long-term randomized control trial data, has demonstrated that growth hormone

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tor of tissue thyroid levels. This may, in fact, help physicians assess tissue thyroid effect with central hypothyroidism and chronic physiologic stress.<sup>118-120</sup> 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.<sup>16,121-123</sup> 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

**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.<sup>4</sup>

All studies that have used central acting stimulation testing in CFS and FM have shown significant hypothalamic-pituitary-adrenal (HPA) axis dysfunction.<sup>4</sup> 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.<sup>4</sup>

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.<sup>7-21,124</sup>

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.

Titration of 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



is generally well tolerated and if such side effects do occur, they usually resolve with a reduction in dose.

Because of the synergistic nature of hormones, small doses of multiple hormones are generally superior to large doses of any one hormone. Each hormone, however, should be started one at a time so we can best monitor for potential side effects.

#### COMPONENT FOUR:

##### Treat the Infectious Components

A great deal of medical literature documents the multiple infections that may either cause or contribute to CFS and FM.<sup>39-48,125-128</sup> Likely, this is due to the immune dysfunction seen with these conditions, which allows opportunistic organisms and other infections to flourish. This includes a variety of viruses such as Epstein Barr (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV6) and intracellular bacterial infections, such as mycoplasma, Chlamydia pneumonia and Borrelia burgdorferi (Lyme disease). Various antimicrobial treatments directed at such infections are significantly beneficial.

#### 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.<sup>2,57-62</sup>

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.<sup>57-62</sup> Heparin can help such patients.<sup>12,58</sup>

Evidence also suggests that neurotoxins are a potential cause or contributing factor to CFS and FM symptoms.<sup>129-131</sup> Visual contrast sensitivity testing and serum C3(a) and C4(a) can help us assess the potential for such exposure.

#### COMPONENT SIX:

##### Maintenance

We need to adjust therapies and wean them to minimal core treatments. With improvement, medications can be discontinued, generally one at a time. During this phase, patients can be seen less often. We generally wean patients off medications before supplements. We also can successfully take patients off narcotic pain relievers. Symptomatic improvement usually correlates with improved cortisol, growth hormone and thyroid levels—so we can adjust hormones as well. However, most patients feel better with the optimal supplemented thyroid levels. Continued thyroid supplementation also appears to prevent relapses.

#### Multisystem Efficacy

A multisystem approach is becoming the standard of care for patients with CFS and FM. And studies are backing this approach. For example, Teitelbaum et al. performed a randomized, double-blinded, placebo-controlled, intent-to-treat study on 72 FM/CFS patients. The goal was to assess the effectiveness of an integrative treatment approach that simultaneously treated the nutritional deficiencies, chronic infections and hormonal dysfunctions that exist with these conditions.<sup>72</sup>

Overall, 90 percent of patients had significant improvements vs. placebo in visual analog scores ( $p < 0.0002$ ), the Fibromyalgia Impact Questionnaire ( $p < 0.0005$ ), the tender point index ( $p < 0.0001$ ) and overall response ( $p < 0.0001$ ) with no significant reported side effects.

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.<sup>4</sup>

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.<sup>87</sup>

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

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