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# *Fatigue*

## **FM's Silent Partner**

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As a symptom, fatigue is no stranger in our society. It's everywhere—so common, in fact, that we may not make special mention of it unless we greatly overextend ourselves or contract a medical condition which ratchets our fatigue up to a level where it can no longer be ignored.

In healthy individuals, fatigue is typically an isolated symptom (rather than part of a multi-system illness) which appears for a short period of time following over-exertion or a long day and is usually relieved by rest or sleep. Fatigue can even be considered “protective”—our bodies' way of keeping us from over-reaching our physical and psychological limits. We quickly learn that if we get tired, it is a good idea to “back off” for a while until we feel refreshed and able to continue on.

Of course, even healthy individuals can suffer acute, disabling fatigue if they continually push too hard at a particular task or activity, deprive themselves of adequate amounts of sleep, skip meals, or become overly stressed. Under such conditions, it is not necessary to have a chronic illness in order to overdo it or have ongoing episodes of fatigue. However, when fatigue is unexplained and does not get better with rest, when it interferes with normal activities, or worsens a co-existing, chronic health condition, then it is usually time to see a physician. This may be more difficult than it sounds, though, because many physicians are simply reluctant to spend a lot of time assessing the symptom of fatigue.

In the foreword to the book, *Fatigue as a Window to the Brain*, Simon Wessely wrote:

“. . . fatigue is unfortunately not a very discriminative symptom for the busy clinician. Doctors afford more attention and respect to symptoms that provide useful diagnostic information, which is arguably their first and most important function—determining what is wrong with the patient.”<sup>1</sup>

He goes on to say:

“Yet for the patient, fatigue is a vitally important symptom. Not just a source of discomfort for its own right, it can also be associated with sometimes profound disruption of physical and mental function, with corresponding impact on quality of life.”<sup>2</sup>

Whether you are an otherwise healthy person trying to investigate symptoms of excessive fatigue

or a patient already diagnosed with a chronic illness which is known to include fatigue among its symptoms, it is not uncommon to face a wall of indifference from health care practitioners or from family/friends who are frankly more impressed by provocative symptoms like pain or rapid heartbeat or a broken leg than the comparatively intangible (even passive) symptom of fatigue.

Wessely also notes that, “As medicine becomes ever more technological and distanced from the bedside, fatigue has not been a fertile topic for those aiming for the glittering research prizes. . .regrettably fatigue studies have so far not figured high on any research funding agenda.”<sup>3</sup>

It is interesting to note that until the scientific revolution of the 19th century, the concept of “chronic fatigue” simply could not exist because at that time symptoms and disease were not distinguished from each other.<sup>4</sup> In any event, what we might consider long-term, pervasive fatigue tended to be lumped with depression.

As common as fatigue is, it's also proven very difficult to define. Dr. John DeLuca states, for example, “In order to truly understand fatigue broadly, one must finally realize that fatigue is a multidimensional construct.” He maintains that it includes at least four components: behavioral (decrease in quality/quantity of performance), feeling state (subjective fatigue), mechanism, and context (environment, attitudes).<sup>5</sup> In fact, a whole range of complex constructs have been offered for fatigue by those who have worked in the field. To mention just a few:

- peripheral fatigue vs. central fatigue
- psychological fatigue vs. physical fatigue
- pathological fatigue vs. normal fatigue
- perceived lack of mental or physical stamina (cognitive fatigue) vs. objective physical performance
- fatigue vs. sleepiness (research suggests they stem from distinct neurological mechanisms)<sup>6</sup>
- “pure fatigue”—does it exist?

It is not the intention of this article to provide an exhaustive critical analysis of the research on fatigue. Rather, its purpose is to explore the factors which can initiate or perpetuate fatigue in a chronic

condition as well as to carefully consider the special characteristics of fibromyalgia (FM) which make its sufferers vulnerable to fatigue.

The emphasis will be on the *symptom* of fatigue which occurs in FM and other chronic conditions rather than the *disease*, chronic fatigue syndrome (CFS), also known as chronic fatigue and immune dysfunction syndrome (CFIDS) or myalgic encephalomyelitis (ME). CFS is a complex and incapacitating disease whose diagnosis is governed by a special case definition (see Table 1) and which has an entire field of research devoted to its study. It is important to note, however, that it is not only possible for the symptoms of FM and CFS to overlap, it is quite common.

### Common Variables Able To Produce Or Exacerbate Fatigue

When an individual has a chronic health condition which already includes a measure of fatigue, the introduction of even commonplace variables like those listed below can cause fatigue levels to escalate and the body's burden to grow. Therefore, the more that a person can minimize, treat, or eliminate these variables, the better.

#### Health Conditions With Fatigue Component

- Infections: viruses, Lyme disease, sinus infections, candidiasis, mycoplasma
- Inflammatory conditions: rheumatoid arthritis, osteoarthritis, polymyalgia rheumatica, lupus
- Allergies
- Endocrine Disorders (hypothyroidism, reactive hypoglycemia/insulin resistance, etc.)

#### Nutritional Factors Which Contribute To Fatigue

- Skipping meals, eating a poorly balanced diet
- Consumption of excessive stimulants in diet: caffeine, alcohol, sugar & sugar substitutes, and refined carbohydrates which irritate muscle and adversely affect the autonomic nervous system and endocrine systems
- Vitamin/mineral deficiency: iron (anemia), magnesium (affects formation of ATP), etc.
- Malabsorption syndromes (Celiac disease)

**TABLE 1**

### Case Definition for Diagnosis of Chronic Fatigue Syndrome

From: Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, and the International Chronic Fatigue Syndrome Study Group. "The Chronic Fatigue Syndrome: A Comprehensive Approach To Its Definition and Study." *Annals of Internal Medicine*. Dec. 15, 1994;121(12):953-59.

**Because there is currently no diagnostic lab test available for chronic fatigue syndrome (CFS), it is necessary to obtain from a patient a complete medical history, a physical exam, a mental status evaluation, a battery of screening tests including blood work and urinalysis, and an assessment of co-existing conditions which may exclude a patient from a diagnosis of CFS.**

**In addition, a case of chronic fatigue syndrome is defined by the presence of the following:**

**1. 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; and**

**2. The concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue:**

- ▶ self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities
- ▶ sore throat
- ▶ tender cervical or axillary lymph nodes
- ▶ muscle pain
- ▶ multijoint pain without joint swelling or redness
- ▶ headaches of a new type, pattern, or severity
- ▶ unrefreshing sleep
- ▶ postexertional malaise lasting more than 24 hours

**Clinically evaluated, unexplained chronic fatigue which does not satisfy the CFS criteria is known as idiopathic chronic fatigue.**

### **Psycho-Social Issues Impacting Fatigue Levels**

- Trying to live up to others' expectations (or one's own expectations) despite health issues
- Trying to keep up with healthy people (denial of illness) or working in spite of pain
- Over-committing to activities, too much stress
- Inability or unwillingness to pace oneself
- Frustration/depression/denial regarding illness

### **Side Effects Of Drugs Cause Drowsiness**

- Drugs for pain, sleep (TCAs, muscle relaxants)
- Other drugs (blood pressure meds, antihistamines)

## **Fibromyalgia & Fatigue**

In a 2002 journal article in *Rheumatic Disease Clinics of North America*, Guymier and Clauw wrote: "Because the physiology of fibromyalgia is not completely understood, the evaluation of fatigue in this setting must first identify and treat better understood conditions."<sup>7</sup> They went on to identify a number of avenues which might be pursued in this vein. Today, we still have much to learn about FM, though there has been some remarkably good new work in the field which has shed a little more light on the nature of fatigue.

We already have a reasonable estimate of the number of people with fibromyalgia and other rheumatic diseases who suffer from fatigue. In a 1996 paper entitled, "The Prevalence and Meaning of Fatigue in Rheumatic Disease," which was published in the *Journal of Rheumatology*, well-known researcher Frederick Wolfe, M.D., stated:

"Fatigue has a special place in rheumatic disorders. It is among the most common symptoms of systemic lupus erythematosus and fibromyalgia (FM) and is a major complaint in ankylosing spondylitis. In rheumatoid arthritis (RA), it is almost a tenet of faith that fatigue is associated with disease activity."<sup>8</sup>

In the study of 1488 consecutive patients with rheumatic disease, which was also reported in his paper, Wolfe used a visual analog scale (VAS) to measure fatigue and found that 76% of fibromyalgia patients had clinically important levels of fatigue as did more than 41% of rheumatoid arthri-

tis or osteoarthritis patients.<sup>9</sup> In addition, the strongest predictors of fatigue were reportedly pain, sleep disturbance, depression, tender point count, and a measure of disability. It is important to note, however, that the relationship between pain and fatigue was independent of depression. The study found that "although depression plays a major role in fatigue, it is not the only factor, and fatigue is present in non-depressed persons; and the same relationship between variables holds in the depressed as well as the non-depressed."<sup>10</sup> Also noteworthy was the finding that fatigue is a powerful predictor of work dysfunction and health status. Wolfe et al., noted: "It is six times more likely that a patient will report being unable to work if he has a fatigue score of two or greater, and it is five times more likely that he will report his health as fair or poor."<sup>11</sup>

## **What Do We Know About The Role Of Fatigue In Fibromyalgia?**

Researchers have known for some time that there are significant abnormalities in the levels of key neurotransmitters in the brain and central nervous system of people with FM. Perhaps best known are Substance P (the agent that signals the brain to register pain), which exists at a level that is three times higher than in normal controls,<sup>12</sup> and serotonin (the agent that modifies the intensity of pain signals entering the brain), which is deficient in FM. Within the neuroendocrine system, abnormal levels of neurochemicals like noradrenaline, dopamine, GABA, and growth hormone have also been recorded. While we know that abnormal levels of these substances exist, it is too early to measure with any precision the direct vs. indirect effects these abnormalities have on the symptom of fatigue. It will first be necessary to have some consensus on the actual definition of fatigue before we can successfully measure it! In the meantime, it is reasonable to hypothesize that the constant, often severe, widespread pain which is diagnostic of FM can cause a great deal of hardship for the body which can ultimately register in the form of profound fatigue.

Rheumatologist Muhammad Yunus, M.D., has also pointed out that FM overlaps with several other associated conditions that share common clinical characteristics and a similar biophysiological mechanism.<sup>13</sup> He calls them "Central Sensitivity Syndromes," (CSS) and includes the FM-associated medical conditions: CFS, irritable bowel syndrome (IBS), tension headaches, migraine headaches, primary dysmenorrhea, periodic limb movement disorder, restless legs syn-

drome (RLS), temporomandibular joint (TMJ) dysfunction, and myofascial pain.

What is interesting about the CSS concept is that all of the member conditions share certain common traits (i.e., pain, *fatigue*, poor sleep, hyperalgesia, etc.) and exhibit neurohormonal dysfunctions which result in central sensitivity which in turn causes amplified, widespread, and persistent pain. With this paradigm, fatigue can be seen in a specific context and is no longer just a stray participant in the pain process.

### Fatigue & Autonomic Nervous System Dysfunction

More recent research in the field of fibromyalgia sheds even more light on the relationship between fatigue and its partner in crime—pain. Manuel Martínez-Lavín, M.D., of the National Cardiology Institute of Mexico (Instituto Nacional de Cardiología Mexico) has used a special form of technology known as heart rate variability testing to demonstrate that the multi-systemic symptoms of fibromyalgia are, in fact, the result of a dysfunction of the autonomic nervous system (ANS) and its peripheral sub-systems, the sympathetic and parasympathetic nervous systems. The autonomic nervous system (ANS) can be defined as “the main regulatory system of the body in charge of maintaining essential involuntary actions, such as the so-called *vital signs* (blood pressure, pulse, respiration, and temperature (among many other variables)).”<sup>14</sup> The ANS works below the level of consciousness and is centrally involved in the “fight or flight” stress response of the body.

Martínez-Lavín and his colleagues believe that there is a “relentless hyperactivity” of the sympathetic nervous system in FM which continues 24 hours a day—particularly at night.<sup>15</sup> (Studies performed in animals suggest that trauma may trigger relentless sympathetic hyperactivity, thus starting a vicious cycle of sympathetic hyperactivity and pain and other symptoms.) However, during times of stress, FM patients also experience a “hypo-reactivity” similar to an over-worked engine which cannot respond to commands for more “juice” when asked to do so. This hypo-reactivity explains the *fatigue*, morning stiffness, dizziness, brain fog, and low blood pressure (orthostatic hypotension) often associated with FM.<sup>16</sup>

Martínez-Lavín maintains, “Relentless sympathetic hyperactivity also explains the sleep disturbances associated with FM. It is known that parasympathetic tone predominates during deep sleep stages and that seconds before awakening episodes, there is

a sympathetic surge. Our concurrent studies of polysomnography and heart rate variability analyses have shown that FM people have relentless nocturnal sympathetic hyperactivity associated with constant arousal and awakening episodes.”<sup>17</sup> These findings give a whole new meaning to the “non-restorative sleep” of fibromyalgia.

### FM, Fatigue & Traumatic Brain Injury

Another area where the symptom of fatigue figures prominently is in the fields of post-traumatic fibromyalgia and traumatic brain injury (TBI). A now famous study by Israeli researcher Dan Buskila, M.D., demonstrated FM was 13 times more likely to occur following a neck injury vs. an injury to the lower extremities.<sup>18</sup> Research by Drs. Donaldson, Esty, and Ochs has also suggested that FM is a “CNS myalgia” resulting from mild traumatic brain injury which, in turn, causes a phenomenon called “EEG slowing” in which the most powerful electrical energy in the brain is in the slowest (delta) brain waves.<sup>19</sup> Why this occurs is not yet known, but it may be that the physical trauma which causes the brain to essentially bounce around in the skull following impact in an accident is partially responsible for altering the biochemistry of the brain and producing some of the symptoms we know as fibromyalgia. In addition, diffuse damage to the brain can cause attentional deficits, slow thought processing, and diminished bilateral integration.<sup>20</sup>

TBI, is of special interest in our inquiry because one of the major problems it causes is fatigue. Unfortunately, the fatigue which results from TBI is different from “simple” fatigue in that it is not fully remedied by sleep or rest. The good news is that researchers at the Neurotherapy Center of Washington and others have had promising results with a treatment known as EEG Neurotherapy which essentially uses a form of high technology biofeedback to “readjust” the brainwaves and restore them to normal functioning.

### Hot Off The Press

New research continues to shed light on the quiet power of fatigue. A University of Michigan study recently demonstrated that FM is in part due to a global disturbance in sensory processing. (*The Journal of Pain*, May 2008) We must certainly wonder to what extent sensory overload translates into fatigue and how it might be related to dysfunction of the ANS. Many of us are already familiar with symptoms of visual overload or multiple chemical sensitivity in FM.

At the University of Iowa, researchers Kathleen Sluka, Ph.D., et al., have discovered through studies of mice that a protein involved in muscle pain works in conjunction with the male hormone, testosterone to protect against muscle fatigue.<sup>21</sup> The study indicates that muscle pain and fatigue are not independent conditions and may share a common pathway that is disrupted in chronic muscle pain conditions. This and other promising research lend hope that there will be better treatments for musculoskeletal pain and fatigue.

### The Treatment Of Fatigue

Because so much remains to be learned about the phenomenon of fatigue, treatment options are somewhat disappointing and largely low-tech. Solid pharmacologic approaches are somewhat limited because drugs, themselves, frequently cause side-effects of fatigue. In terms of autonomic nervous system dysfunction (dysautonomia), it is important to recognize that many drugs used for FM also have “autonomic consequences,” and that pharmacological therapies need to be reserved as much as possible for special situations where it is necessary to improve a patient’s quality of life (e.g., when sleep-inducing medications or medications for severe pain or anxiety are needed).<sup>22</sup> Drugs which raise central levels of norepinephrine or dopamine are of most interest for fatigue but are still being studied.<sup>23</sup>

Cognitive behavioral therapy (CBT) which combats maladaptive behaviors and negative or catastrophic thinking is a popular treatment recommended for fatigue. However, because various forms of CBT are available, it is often difficult for patients to know which form to try. Dr. Edward Shorter offers the following “tongue-in-cheek” insight about CBT:

“Today the most effective remedy psychiatry has to offer for chronic fatigue seems to be cognitive behavioral therapy (CBT)...Yet this technique requires the patient at some level to accept that his symptoms have a psychogenic component... Fatigue has thus passed from being a ‘real’ disease, as treatable as constipation, to a nondisease that is treatable only with elaborate programs of psychotherapy that many fear. One is inclined to ask, ‘Is this progress?’”<sup>24</sup>

Ironically, the therapy with one of the best track records for fatigue is graded aerobic exercise. It helps to build stamina, reverses the cardiovascular deconditioning which results from inactivity, and

elevates mood. Because aggressive exercise is usually counter-productive in FM patients, low-impact exercise (via aquatics, walking, or treadmill work) is usually recommended. Also useful are relaxation techniques, biofeedback, and breathing exercises (i.e., the use of “belly breathing” to combat shallow breathing). Alternative medicine techniques like acupuncture, yoga, and Qi-gong have also proved helpful.

Finally, it is crucial to remain vigilant of factors which can magnify and/or perpetuate fatigue in fibromyalgia and in related conditions like myofascial pain, IBS, and TMJ. Pacing of activities, schedule management, stress reduction, delegation of tasks to others, reasonable self-expectations, sensible nutrition (avoiding ANS-irritating stimulants), and common sense will help relieve the body of heavy burdens and go far in lessening fatigue.

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