

Fibromyalgia Description

Fibromyalgia (FM), pronounced: *fy-bro-my-AL-ja*, is a chronic, body-wide pain disorder. FM can exist by itself, but is usually coupled with other symptoms such as:

- severe daytime fatigue
- un-refreshed sleep (likely due to a number of sleep anomalies)
- irritable bowel syndrome
- chronic headaches
- morning stiffness
- cognitive or memory impairments
- reduced coordination
- decreased physical endurance

The American College of Rheumatology published the diagnostic criteria for FM in 1990. This selection criterion was shown to be 88% accurate in identifying patients with this syndrome. Researchers have noted a significant overlap between FM and chronic fatigue syndrome (CFS). A majority of these patients meet both the diagnostic criteria for FM *and* the CDC criteria for CFS. In fact, the American Association for CFS has elected to combine the two syndromes as part of their research education mission.

FM experts estimate that about 10 million Americans and approximately 3-6% of the population worldwide suffer with FM. While it is most common in women, the illness strikes men, women, and children of all ages and ethnic backgrounds. For those with severe symptoms, FM can be extremely debilitating and interfere with even routine daily activities.

Chronic Fatigue Syndrome / Myalgic Encephalopathy Description

Chronic Fatigue Syndrome / Myalgic Encephalopathy (CFS/ME) is a poorly understood, highly debilitating disorder of unknown cause. **Myalgic** - *meaning muscle* - indicates the pain involved in the muscles. **Encephalo** - *meaning brain* - indicates that the brain functioning is involved. **Pathy** – *the word for sickness or illness*. CFS/ME is marked by chronic mental and physical exhaustion, often severe, and by other specific symptoms, arising in previously healthy and active persons. Despite promising avenues of research, there remains no objective pathological finding which is widely accepted to be diagnostic of CFS/ME. It remains largely a diagnosis of exclusion, made on the basis of patient history and symptomatic criteria, although a number of tests exist which can help aid diagnosis.

Demographics

FM experts estimate that about 10 million Americans and approximately 3-6% of the population worldwide suffer with FM. While it is most common in women, the illness strikes men, women, and children of all ages and ethnic backgrounds. For those with severe symptoms, FM can be extremely debilitating and interfere with even routine daily activities. It is estimated that the average care cost per patient per year is close to \$2,300.

Chronic Fatigue Syndrome/Myalgic Encephalopathy (CFS/ME) is a highly debilitating disorder thought to affect approximately 4 per 1,000 adults in the United States and other countries, and a smaller fraction of children.

Research studies indicate that the average FM and/or CFS/ME patient takes three different drugs daily in an attempt to control their symptoms, yet no single therapeutic agent was found to be effective in relieving the symptoms during the seven-year duration of the study (1989 to 1996).

Disability Studies

Four reports have shown that FM can be as disabling as rheumatoid arthritis (RA). RA is listed in the Social Security Disability law book, and while FM pain is acknowledged, the condition is not specifically listed. Due to the difficulties in gaining recognition for FM as a disabling illness, the percentage of patients drawing SSD payments based on FM is only 16.2%. Yet, nearly 30% of FM patients claim that they cannot hold down a steady job due to this condition. The total yearly drain on the U.S. economy is estimated to be over \$20 billion. Preliminary findings indicate that the cancer risk is also doubled in people with FM.

Patients with CFS/ME report critical reductions in levels of physical activity with impairment comparable to other fatiguing medical conditions including multiple sclerosis, late-stage AIDS, lupus, rheumatoid arthritis, heart_disease, end-stage renal disease, chronic obstructive pulmonary disease (COPD), and the effects of chemotherapy. The severity of symptoms and disability is the same in both genders with strongly disabling chronic pain, but despite a common diagnosis, the functional capacity of individuals with CFS/ME varies greatly. While some lead relatively normal lives, others are totally bed-ridden and unable to care for themselves. Employment rates vary with over half unable to work and nearly two-thirds limited in their work because of their illness. More than half were on disability benefits or temporary sick leave, and less than a fifth worked full-time.

Research Findings

Pain is the predominant feature of FM and CFS/ME, but its cause is unknown. Significant abnormalities in the central and peripheral nervous systems have been uncovered in recent years and most researchers in the field consider FM and CFS/ME to be a central pain state (e.g., central sensitization). Substance P (SP) in the spinal fluid is three times that of normal healthy people. Nerve growth factor (NGF) in the spinal fluid is four times that of healthy people. Increased production of nitric oxide in the spinal fluid and in the peripheral blood of FM and CFS/ME patients has also been found. Pro-inflammatory cytokines are excessively produced in patients with FM and CFS/ME, pointing to an immune system Th1/Th2 axis disruption.

The 2003 study by Ali Gur et al. demonstrated that the cytokine elevations correlated with abnormalities in brain blood flow based on SPECT scan analysis. Gur's 2002 study showed that elevated IL-8 levels corresponded with pain intensity. It is proposed that pro-inflammatory cytokines produced by activated glial cells within the central nervous system may play an aetiopathogenetic role in FM and CFS/ME.

Indeed, IL-8 has been implicated in a genetic profiling study using micro-arrays in patients meeting the CFS/ME criteria. Although the findings of elevated SP and NGF are substantial, recent research by the author of the NGF finding (Alice Larson, Ph.D.) clearly indicates that elevated SP and NGF are not at the heart of the etiology of FM and CFS/ME. In fact, NK1 receptor antagonists are only likely to help FM and CFS/ME patients when they are co-administered with an upload and noradrenaline (whose metabolite is abnormally low in the spinal fluid of FM and CFS/ME patients - and the same holds true for serotonin and dopamine).

FM/CFS/ME FACT SHEET

Other significant abnormalities in FM and CFS/ME patients include:

- Sleep disorder.
- Autonomic nervous system dysfunction.
- Elevated activity of CRH neurons which is believed to cause disruption of many hormonal axes including the HPAaxis.
- Impaired brain blood flow to the thalamus and other pain-processing centers.
- Substantially reduced production of growth hormone overall, and additional blunting of growth hormone during exercise.
- Failure of the diffuse noxious inhibitory control (DNIC or spatial summation) to respond to a painful stimulus.
- Abnormal windup (or temporal summation) at rest and significantly exacerbated windup during exercise, which may explain the exercise intolerance that FM patients exhibit.

Current Status of Research Spending by NIH

Most FM and CFS/ME research at NIH (National Institute of Health) is sponsored by NIAMS (National Institute of Arthritis, Musculoskeletal and Skin diseases). The 1997 FM and CFS/ME research funding level at NIAMS measured out to only 0.6% of their annual budget of \$257 million - not much for the second most common rheumatic disease.

That same year, however, NIH created a Special Emphasis Panel (SEP) specifically for the review of FM and CFS/ME research grant applications, and this continues to lead to increased funding for the condition. In 1999, the National Institute of Neurological Diseases and Stroke (NINDS) and the Department of Defense (because of overlapping conditions such as Gulf War Illness) became involved in funding research on FM and CFS/ME as well.

While the increase in research funding on FM and CFS/ME is encouraging, the NIH funded research projects are, for the most part, still not focused on the patient-relevant issue of providing improved therapy options. A review of the NIH online Computer Retrieval of Information on Scientific Projects (CRISP) system abstracts confirms that less than 10% of government sponsored research on FM and CFS/ME pertains to therapeutic interventions. However, the combined NIH and DOD expenditures on FM and CFS/ME-related research are estimated to be roughly \$7 million annually.

Recent Therapeutic Success

At the October 2002 American College of Rheumatology (ACR) meeting, several researchers presented successful treatment trials in FM and CFS/ME patients. In particular, a multi center pregabalin study demonstrated that FM and CFS/ME is a condition that can be evaluated and that clinical improvement is possible.

Single bolus doses of fentanyl and dextromethorphan (tested individually) were documented to show clinical improvement and were also capable of substantially reducing windup in people with FM and CFS/ME. However, highly effective therapies that specifically target the central pain state in FM and CFS/ME patients are in high demand. Human growth hormone, a therapy that targets problems in the peripheral tissues, was shown in a nine month trial to be helpful in reducing muscular pain and relieving problems of exercise intolerance. A novel immune modulation Staphylococcal vaccine-type therapy to target the cytokines in the periphery has also shown effectiveness.

Sodium Oxybate (a compounded version of the natural brain chemical gamma-hydroxybutyrate) has been tested in a placebo controlled crossover trial involving 17 overnight sleep tests for each of the 20 FM and CFS/ME participants and showed amazing results. It produced significant increases in slow-wave sleep, decreased alpha-wave intrusion, decreased pain, and is suspected to also increase growth hormone secretion during sleep. The high prevalence, disability rate and health care costs associated with FM and CFS/ME should be motive enough to encourage the pharmaceutical industry to become involved in developing effective therapies for this condition.

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