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FIBROMYALGIA

A Biochemical View and New Approaches

The Latest and Best Clinical Information Attained from World Leading Authorities

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WHAT IS FIBROMYALGIA?

Fibromyalgia is an anomaly. It is a condition still not fully understood and in some instances not accepted by mainstream medicine, although **The <u>American College of Rheumatology recognizes and defines it as a disease</u>**. Fibromyalgia is characterized by chronic widespread pain involving more than three segments of the body, including the presence of at least 11 of 18 specifically designated tender points. The term "fibromyalgia" actually means pain in fibrous and muscular tissues. It is a disorder involving brain chemicals and in reality, is a collection of symptoms with no measurable cause. Although it has existed since Victorian times and has been known by other names such as neurasthenia, chronic rheumatism and fibrositis, today it is referred to as fibromyalgia syndrome, or simply FMS.

While the **<u>primary physical symptom is widespread body pain</u>**, other symptoms may accompany the disorder. These include morning stiffness, general fatigue, cold sensitivity, exercise intolerance, poor sleep, dizziness, numbness or tingling of the extremities, headaches, pruritis, fluid retention, bowel discomfort, irritability, depression, anxiety and mood swings.[1,2,3] Aching occurs most commonly in areas around the neck, shoulders, upper and lower back and hip areas.

There are many similarities between FMS and Chronic Fatigue Syndrome, or CFS (another medical mystery). Statistically, 70% of patients with FMS also meet the CDC criteria for CFS and 67% of patients with CFS meet The American College of Rheumatology (ACR) criteria for FMS.[1] Similarities include debilitating fatigue, muscle and joint pain, digestive problems, headaches, sleep problems, anxiety, allergy sensitivity, restless leg syndrome, mental confusion and depression. Patients have described CFS as "flu-like" and fibromyalgia as "aching all over".[3,4] Fever and swollen glands occur in a higher percentage of CFS patients than in FMS. The most severe complaint for CFS patients tends to be around-the-clock fatigue which does not subside, while in FMS patients it is around-the-clock pain which rarely subsides. Cognitive impairment is more significant among CFS sufferers than in cases of FMS.[6]

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Although there are biochemical differences in the body between the FMS and CFS, there is no tangible diagnostic tool such as a lab test or x-ray that can be used to confirm diagnosis. This creates a dilemma for those who suffer from these diseases. They may exhibit symptomatology for years before a diagnosis is made. Even after diagnosis, many patients are still ostracized by the traditional medical community (who has not taken time to learn more about this disease), seen as having a disease that's "all in the head". Although FMS and CFS share many of the same symptoms and are often diagnosed together, the intent of this article is to differentiate the two and shed light on the disease known as fibromyalgia.

Clinical features of FMS and their frequency of occurrence are as follows:[45]

- 90-100% experience generalized pain, stiffness and morning fatigue.
- 70-90% experience sleep disturbances, morning stiffness, tenderness, post-exertional malaise, numbness and tingling, tissues feeling swollen, cognitive impairment, vertigo, headaches, dry mouth, dysmenorrhea and increased sensitivity to noise, odors and stress.
- 50-70% experience allergies, arrhythmias, changeable facial expressions and mood, irritable bowel syndrome, visual disturbances, cold intolerance with cold extremities and fever or feeling feverish.
- 15-50% experience muscle twitches, restless legs, night sweats, skin disorders such as unexplained rashes, itchy patches, auditory disturbances, propensity for infections, breathing problems, interstitial cystitis, TMJ and multiple chemical sensitivities.
- Less than 15% experience concurrent depression.

STATISTICS

While all ages and both sexes get FMS, it is **predominantly found in women.** Typical onset occurs between the ages of 29 and 37 and it is diagnosed at ages 34 to 53. In other words, many patients suffer for long periods of time before a proper diagnosis is established.[5] In the United States, FMS is estimated to occur in approximately **3-6% of the population**, and 86% of sufferers are women.[3,5,6,7] Onset is usually gradual and associated with some type of trauma, either physical, mental or emotional.

FMS can be debilitating. Studies show that 40% of Americans with FMS are able to maintain employment with a decrease in level of function, 30% with a change of jobs, 17% quit their jobs and **one-third become partially or totally disabled**.[3,5,8]

Among children, fibromyalgia occurs in about 45% of the total pediatric rheumatology patients seen in private practice. In the pediatric FMS population, 67% of patients average evaluations by three or more doctors prior to diagnosis, 60% are misdiagnosed with juvenile chronic arthritis, 20% are misdiagnosed with growing pains, 7% with hysteria and 7% with psychological disorders.[6]

HORMONAL/METABOLIC ABNORMALITIES

Clinical studies have indicated **biochemical metabolic abnormalities; sleep disturbances and alterations in the nervous, immune and muscular systems** in FMS. Some of the identified biochemical changes include significantly decreased levels of serotonin, calcitonin and prostaglandin E2 as well as a significantly increased level of prolactin.[10] FMS patients have been found to have elevations in basal values of Adrenal Corticotropic Hormone (ACTH), cortisol and Follicle Stimulating Hormone (FSH). Decreased basal values of insulin-like growth factor I (IGF-I), triiodothyronine (T3) and estrogen have been noted.[10,15] Many patients show increased pyruvate and decreased lactate production.[108]

Endocrine System- Review

Prior to exploring these abnormalities, it is important to understand the role of the endocrine system. Briefly, an endocrine cell is the site of hormone synthesis. These hormones are stimulated by chemical precursors secreted by the body cells and transported through the blood. Once synthesized, hormones are then released back into the blood, where they bind to proteins. The blood delivers the hormones to target cells to exert their action. Once a hormone has performed its function, most are deactivated or excreted by the liver or kidneys.[13]

Afferent input stimulates the endocrine cell to produce more hormones. Although continual, the rate of secretion is rarely constant and plasma concentration is dependent upon hormonal secretion and excretion. Thus anything that interferes with either process can alter hormone levels within the body. Other factors involved in hormonal stimulation of cellular function include enzyme activity and rate of membrane transport.[13]

Most hormones come from the hypothalamus, anterior and posterior pituitary, adrenal cortex, adrenal medulla, thyroid, parathyroid, thymus, pineal, gonads, pancreas, kidneys and the GI tract. Hormones are **involved in every activity and function of the body** either directly or indirectly, serving as messengers that regulate cellular function.[13]

The HPA Axis in FMS

The hypothalamic – pituitary – adrenal (HPA) axis has been studied in depth and abnormalities in FMS patients have been discovered. The HPA axis is the regulatory system most central to the stress response. An alteration in the HPA axis can theoretically affect all the hormones and regulatory systems involved in the stress response. This can create a domino effect

on other systems of the body due to the interconnected nature of the endocrine and neurological systems. In order to understand the relevance of these findings, a review of the interrelation of these glands and their hormones is in order.

Pituitary

The **pituitary gland** sits directly behind the sphenoid sinuses, just below the hypothalamus, to which it is connected by a "stalk" of neurons and blood vessels. It is comprised of three lobes: anterior, intermediate and posterior.

The **anterior pituitary, often called the master gland**, is comprised of true glandular tissue. It produces at least six different protein hormones, the secretions of which occur independently of each other. These six hormones are:

(1) **TSH**, or thyroid stimulating hormone, which stimulates thyroid hormone secretion (primarily thyroxine)

(2) **ACTH**, or adrenocorticotropic hormone, which stimulates the adrenal cortex to secrete cortisol

(3) **Prolactin**, which targets the breasts and has immunomodulatory activity

(4) **GH**, or growth hormone, which exerts an array of metabolic effects upon many organs and tissues

(5) **FSH**, or follicle stimulating hormone (in gonadotropic hormone)

(6) **LH**, or luteinizing hormone (in gonadotropic hormone)[13]

Understanding the control mechanisms in relation to anterior pituitary hormone secretion is key to comprehension of the complexities involved in the axes of hormonal regulation. One control is negative feedback. For example, when ACTH stimulates cortisol secretion, it increases serum cortisol levels, which in turn acts upon the anterior pituitary to inhibit ACTH secretion. The same occurs with the thyroid and sex hormones and their respective pituitary hormones.

Hypothalamus control over the release of anterior pituitary hormone comes from the **hypothalamus**. The hypothalamus produces hormonal substances called releasing factors or releasing hormones. Hypothalamic neurons secrete these releasing substances into the **capillary system of the pituitary** (there are no neural connections to facilitate this). All these substances except for one, the prolactin-inhibiting factor, are stimulatory.[13]

Receiving both facilitory and inhibitory neural input from all areas of the body, the hypothalamus thus controls the secretion rate of the releasing factors. The influence of stress or anxiety alters hypothalamic activity, which then generates an endocrine disorder that leads to infertility.[13]

While the anterior pituitary is true glandular tissue, the posterior pituitary is actually true neural tissue and is an outgrowth of the hypothalamus. Though released from the posterior pituitary, **ADH and oxytocin are synthesized by the hypothalamus, which directly releases them, along with hypothalamic releasing factors into the appropriate pathways.** If the posterior pituitary is surgically removed, the resultant loss of oxytocin and ADH secretion is temporary as capillaries soon develop along the connecting stalk to the hypothalamus and hormone release returns to normal levels.[13] **Hypothalamic releasing factors/ hormones directly control the release of growth hormone (GH), TSH, ACTH, FSH, LH and prolactin.** Arginine vasopressin (an ACTH secretagogue) and **CRH (cortico releasing hormone) are key hypothalamic elements in HPA axis regulation.**[18]

Beyond the production of melanocyte-stimulating hormones, intermediate lobe function is unclear. As we know, melanocytes determine pigmentation of the skin. This may or may not be a factor to investigate if future studies indicate a predisposition to FMS based on race.

Adrenals

The **adrenal glands** are pea-sized, and one sits atop each kidney. The inner portion, the **adrenal medulla**, comprises about ten percent of the adrenal gland and is responsible for **epinephrine secretion**. Epinephrine is the "fight or flight" neurotransmitter that places the body on a high alert. In FMS, this state of alert is constantly stimulated. Thus, the adrenal medulla eventually grows tired, becomes sluggish and wears out. This explains why FMS patients are often fatigued yet can't fall asleep.[50]

The **adrenal cortex**, the larger outer portion of the adrenal gland, secretes several **steroid hormones**. The most important of these are:

(1) **Aldosterone**, a mineralocorticoid which maintains the sodium:potassium balance. Aldosterone is under the control of non-pituitary influences, primarily other hormones and potassium and sodium serum levels.[13]

(2) **Sex steroids**

(3) **Cortisol**, a glucocorticoid because of its role in carbohydrate and protein metabolism. Cortisol is responsible for many other functions within the body. It is **under the control of ACTH** and aldosterone.

There is evidence to support a **dysfunction of the HPA axis in FMS that is characterized by alterations in cortisol production and its feedback response.**[9] Diminished ACTH and epinephrine responses to hypoglycemia indicate an impairment of the hypothalamic-pituitary activity of the HPA axis and cortisol production.[11,12,16] Stimulating the HPA axis function in FMS via CRH and insulin-induced hypoglycemia indicate a hyperreactivity of the ACTH response.[16,18] With this increased ACTH release, a subsequent hyporesponsiveness of the adrenals occurs in FMS. This diminished response to CRH generates increased secretion of CRH. In FMS, the same response has been observed in exercise with a consequent alteration in the growth hormone – IGF1 — somatomedin C correlation.[12,14] CRH activates the pituitary-adrenal axis and stimulates somatostatin secretion at the hypothalamic level. This in turn inhibits the releasing factors of the hypothalamus, has an effect on GH, TSH and gonadal hormone functions.

Studies of 24-hour urinary cortisol levels of patients with FMS clearly demonstrate a hyperreactive ACTH release in conjunction with a hyporesponsiveness of the adrenal glands. In order to achieve the same amount of adrenocortical output of cortisol as controls, a significantly higher level of circulating ACTH is required. Based on these studies, **diminished adrenal secretion seems to be a consistent feature of FMS**.[12,16] These findings have implications for CRH, GH and vasopressin secretion as well. FMS patients exhibit **diminished sympathetic nervous system activity**, which may be a contributor to this HPA alteration – the sympathetic outflow from the hypothalamus via the spinal projections to the adrenal is impaired. It is also possible that the resistance of the adrenal glands is related to a glucocorticoid receptor dysfunction.[12,16] Put simply, the HPA disturbance that occurs in FMS is really an interference of the negative feedback mechanisms wherein the adrenal cortex is resistant or hyporesponsive to ACTH, which results in stimulation of the pituitary and hypothalamus glands to secrete more ACTH. This then creates a **hyperreactivity of the hypothalamus and pituitary**.

The most significant factor in this HPA dysregulation is the fact that **adrenocortical insufficiency can lead to the fatigue and sleep disturbance** so commonly seen in FMS. It also affects brain structures involved in regulating mood, and the level of depression in FMS patients corresponds with the degree of HPA disturbance.[17,19] Low cortisol levels could also explain the impaired muscle performance and decreased aerobic capacity associated with FMS. Increased pain perception is also created by hypocortisolemia.[11]

Another study by Crofford, et.al.[18] on HPA axis regulation in FMS also found low 24-hour urinary cortisol levels. However, total and free plasma levels collected in the evening were significantly elevated. This study found basal ACTH levels to be insignificantly elevated, but **peak ACTH levels were much higher in FMS than in controls**. Morning total and free plasma cortisol levels were not significantly different from healthy controls.

Neuropeptide Y (NPY), an amino acid neurotransmitter, is also found to be significantly lower in FMS. NPY is involved in the regulation of circadian rhythms, the stress response, sexual function, and some cardiovascular functions. It may also be involved in feeding behaviors. Thus, all these alterations in the HPA axis contribute to a loss of the normal diurnal flow and generate other irregularities and symptomatologies.[14,19]

Diminished adrenal secretion seems to be a consistent feature of FMS.

The fact that cortisol secretion is pulsatile could explain the variant results of these studies. A **24-hour urine collection does not reflect the rhythm of the cortisol pulse**. Normally there are **8-9 cortisol peaks over a 24-hour period**, probably in response to basal ACTH and CRH surges. The height of the peaks could be normal in FMS but the frequency diminished, which would be reflected in a low 24-hour urinary cortisol specimen.[18] FMS patients exhibited a magnified and prolonged ACTH response to CRH, which suggests a defect in cortisol control in spite of free cortisol levels being similar to controls.[12] It has also been theorized that the hypothalamic CRH neurons not only play a key role in the deviations of other hormonal axes, but also in the pain response and psychological mechanisms.[19]

Although it has not been determined if the low cortisol and the associated symptoms are a primary feature of FMS, the **collective data clearly suggests a primary adrenal insufficiency**. However, low endogenous CRH production can lead to adrenal cortical atrophy, with resultant adrenal insufficiency. Diminished sympathetic input to the adrenals will also create adrenal insufficiency through a reduced feedback signal, which allows the hyperreactive ACTH response.[12,30]

IGF-1 and Growth Hormone in FMS

IGF-1 and growth hormone are highly interrelated. IGF-1 is produced in the liver, and its production is stimulated by GH. If liver function is impaired, IGF-1 production will decrease. IGF-1 is a factor responsible for stimulating the growth of muscle, bone and cartilage tissues. It is the primary mediator of GH's anabolic activity and is a **prerequisite for normal**

muscle maintenance.[18,20,21,26] Thus, low IGF-1 can be an indicator of low GH secretion and consequent impaired metabolic processes of the muscle, bone and cartilage. IGF-1 has been **found to decline with age, stress, hormone replacement therapy, and elevated serum insulin levels**.[22,23,24,29,41] Studies have consistently indicated low IGF-1 levels in individuals with FMS. It is important to note that GH has a very short half-life and measurements of IGF-1 rather than GH may be more reflective of GH deficiency.[26,28,29]

When GH was injected daily, a prompt and sustained increase in IGF-1 levels occurred. Over six months, significant improvement in symptomatology and tender points was exhibited. However, once GH administration was eliminated, symptoms worsened.[25,26,27,38] (GH therapy is also too expensive to be a routinely used therapy for most people.) Abnormalities in GH secretion could also explain the carbohydrate metabolism impairment that is seen in FMS.[108]

Maximum GH secretion occurs during stage 4 sleep and researchers have found significant decreases in nocturnal GH secretion in FMS patients.[29] These two facts may explain why the poor sleep habits of FMS patients cause degeneration of the condition.

Other consequences of GH deficiency include **reduced skeletal muscle mass, impaired myocardial contractility, a reduced plasma volume and decreased psychological well-being**. These are manifested in the symptoms of decreased capacity for strenuous exercise, low blood pressure, cold intolerance, low energy, low grade depression, decreased libido, emotional lability (facial expressions) and increasing social isolation. These and similar symptoms are often hallmarks of FMS.[22]

Serotonin in FMS

Serotonin deficiency is another abnormality discovered in FMS. Serotonin levels are important in **sleep regulation, aggression, libido, mood, anxiety, appetite, temperature and pain sensation**. Chocolate cravings may be an indicator of a serotonin deficiency.[36]

Deficiency is thought to be due to poor GI absorption of the precursor amino acid tryptophan.[31] Serotonin, along with tryptophan, is a precursor to melatonin (MT), which is secreted by the pineal gland. FMS patients have been found to have as much as **31% lower MT secretion and 36% lower peak serum-MT values** during the hours of darkness as healthy individuals.[36] These deficiencies can contribute to sleep disorders, daytime fatigue and altered pain perception.[32] Deficiencies of precursors to MT can account for a serum-MT deficiency as well as impaired sleep processes, increased urinary excretion, decreased nocturnal MT secretion and increased hepatic and/or renal degradation of MT. The most likely cause of MT deficiency in FMS is a serotonin/tryptophan deficiency. Serotonin antibodies have also been detected in patients with FMS, which could impair synthesis of active MT and decrease nocturnal release.[32]

Studies directly link the pressure tenderness and number of tender points in FMS to serotonin levels.[44,18] Serotonin is known to influence the circadian rhythms of the HPA axis, and a correlation of free serum tryptophan levels has been linked to pain severity in FMS.[18,33] Low serotonin in FMS corresponds with the number of tender points in FMS.[33,34] Improvements in the symptoms of somatic pain, depression, anxiety and insomnia have occurred with serotonin supplementation in FMS.[35]

Studies have shown that 50-74% of FMS patients have developed antibodies to gangliosides.[53,54,55,56] Gangliosides are a key component of the serotonin receptor. Thus, serotonin disturbances may be a factor in these irregularities. Serotonin is required to activate Immune NK cells and, as previously noted, serotonin is deficient in FMS. It is interesting to note that patients with other rheumatic disorders such as rheumatoid arthritis and collagen diseases do not have anti-serotonin antibodies. It has not yet been determined if these antibodies are pathogenetic, but family members of FMS patients were also observed to have them.[56] CFS patients also have these antibodies, although levels are not as high as in patients with FMS.

Another correlation has been discovered with the presence of these antibodies in patients with inner ear disorders such as sudden deafness and progressive hearing loss. Approximately 50% of patients studied displayed symptoms typical of FMS and CFS, indicating that those patients with hearing disorders may also have undiagnosed FMS or CFS.[55]

These abnormalities in antibody production may potentially account for the increased occurrence of allergies and chemical sensitivity in FMS.

A defect in serotonergic and adrenergic systems is a characteristic of migraines. Migraine headaches are a common occurrence among FMS sufferers. This fact seems to parallel the significant serotonergic system failures and adrenergic transmission defects evidenced in FMS.[40]

Thyroid Function in FMS

Other endocrine abnormalities indicated in FMS involve the **thyroid**. Cold sensitivity, chilliness, low blood pressure and constipation are all signs of hypothyroidism. Studies of FMS confirm an alteration in thyroid hormonal response and secretion rates. In one study, FMS patients displayed a blunted thyrotropin secretion rate and a blunted response of the thyroid hormones to thyroid releasing hormone (TRH). This is suggestive of a decreased hypothalamic response.[30,39] When Neeck and Riedel[31] studied the HPT (hypothalamus, pituitary, thyroid) axis in FMS patients, they discovered not only the blunted TSH response, but also a simultaneous increased secretion of prolactin and a decreased secretion of free triiodothyronine (T3) and free thyroxine(T4). This type of hormonal profile can be caused by a failure of T4 to T3 in the peripheral tissues or within the pituitary.[19] Overproduction of cortisol can inhibit the conversion of T4 to T3 and decrease the responsiveness of TSH to TRH, pointing to the abnormal HPA axis. Thus, **these hormonal changes can be elicited by stress** and the degree of low serum T3 levels directly corresponds to the level of stress.[19,39,42,43]

Gonadal Function in FMS

Abnormalities have also been noted in **gonadotropin hormones** in women. Pain sensitivity alterations coincide with changes in the gonadal hormone levels with as much as 72% of women reporting a worsening of symptoms premenstrually.[46,47] A study by Hapidou and Rollman[46] revealed **variations in tender point count during the menstrual phase** but stable pain thresholds. They discovered that tender points increase during the follicular phase and decreased during the luteal phase.

Fluctuations in platelet serotonin levels normally occur in relation to the menstrual cycle. The highest levels occurring during the follicular phase.[46,48,49] **Cyclic variations in serotonin levels can modulate tender points**, another correlation of an endocrine axis relative to the serotonin deficiencies found in FMS. It would point to the need to **consider menstrual status in a woman when evaluating tender points**.[46]

Most women with FMS experience a worsening of symptoms during menopause.[50] When Ostensen, Rugelsjoen and Wigers[47] studied women in relation to FMS and pregnancy, all except one patient experienced a **worsening of symptoms with the third trimester**. Breastfeeding and the return of menses seemed to have no influence on the course of the disease. **Miscarriage was also found to be more prevalent among women with FMS**.

The Immune System

In the immune system, the HPA axis is once again the key. One of the major roles of the HPA axis is restraining the immune system and preventing tissue damage. When the HPA axis is activated, it becomes immunosuppressive and is involved with various interleukins and releasing factors. The hypothalamus-pituitary-thyroid axis (HPT) also becomes involved. Tumor Necrosis Factor (TNF) and interleukin (IL-1) are activated through the HPT axis, which then creates a relevant decrease in TRH, TSH, T3 and T4. The cytokines (immunoregulatory substances secreted by cells in the immune system) involved also have receptor sites in the brain and work at other cellular levels. Thus, **immune system abnormalities can create alterations in mood** and so on.[137]

The tone of the immune system and regulation of inflammatory responses are directly or indirectly affected by the gonadal axis, via the HPA axis. As we have seen, the effects of the HPA axis on the gonadal axis are relevant to attempts at homeostasis during stress. It is thought that these interactions may be a **fundamental element in the generation and continuation of autoimmune diseases**.[51] Such defects have been observed in autoimmune and rheumatic diseases, chronic inflammatory diseases, chronic fatigue syndrome and fibromyalgia. Indeed, **gonadal and thyroid hormone levels decrease during severe inflammatory disease**. In some forms of autoimmune disease, prolactin levels are elevated and in others the bioactivity of prolactin is diminished.[52] The hypothalamus-pituitary-ovarian (HPO) axis becomes involved. When progesterone, estrogen and prolactin levels are altered, the immunological response is altered. These hormonal changes can create physical and mental changes.[137] It is also thought that there may be some neural defects in the regulation of inflammation. Up to 85% of FMS patients have also been found to have abnormal immune complex deposits at the dermal-epidermal junction.[5]

The Neuromusculoskeletal System

Physiological alterations noted in FMS include less handgrip strength, decreased isokinetic muscle torque of knee extensors (41-66%), decreased muscle relaxation rate (a good measure of muscular metabolic rate), increased muscle fatigueability, increased muscle tension and stiffness, impaired microcirculation and mitochondrial damage.[58,59]

Some **abnormalities discovered in the muscles** of FMS patients include histological alterations, edema,

increased interstitial fluid, increased lipid content, degeneration and alterations of muscle fibers and swollen mitochondria.[5] The most common musculoskeletal abnormality in longstanding FMS is known as type II fiber atrophy (fiber breakdown). Low levels of high-energy phosphates, decreased ATP and ADP levels and low phosphorylcreatine have also been found.[57]

Muscular microcirculation is controlled by ADP metabolites, the sympathetic nervous system and humoral factors. Muscle biopsies have revealed decreased ATP and phosphocreatine (PC) levels in individual muscle fibers of FMS patients. This would also contribute to an energy crisis within the muscle relevant to ADP.

Studies by Olsen and Park[59] support many of these findings and offer varied histological evidence of skeletomuscular abnormalities. 73% of FMS patients whose trapezius muscles were biopsied exhibited muscle fibers with a **"moth-eaten" appearance**. Approximately 25% had ragged red fibers in their muscle tissue, a pathological alteration that is usually associated with mitochondrial myopathies.[60] Quadricep muscle biopsies revealed **bandlike structures, or rubber-band morphology**, associated with constriction of underlying muscle fibers. It is speculated that these structures lead to prolonged muscle contractions and correlate with increased pain and stiffness evidenced in FMS. This also interferes with total oxidation of muscle tissues and can be supported by the fact that FMS patients with these fibers also had a lower number of capillaries in both trapezius and quadriceps tissue. Electron microscopic examination of the trapezius muscle tissue also showed **thickening and structural damage of the capillary endothelium**.[59]

Sufferers of FMS have impaired aerobic endurance possibly related to the impaired oxygenation and decreased blood flow. In addition, the already low ATP and PC concentrations decreased even more during exercise.[59] Decreased ATP levels have also been demonstrated in erythrocytes of FMS, which would suggest the ATP defect may be systemic and general rather than localized.[59]

Collagen cross-links have also been studied in FMS. Metabolic byproducts of collagen cross-linking were found to be lower than in controls. These are indicators of **connective tissue and bone degradation** and can contribute to the remodeling of the extracellular matrix and deposition of collagen around the nerve fibers in FMS. This also contributes to the lower pain threshold at tender points.[61]

The primary factor relevant to pain in FMS seems to be the nociceptive component of the nervous system. Nociception is the process of pain transmission from the periphery via receptive or afferent neurons. Various mechanisms of nociception are involved and it is important to understand the process by which pain sensations occur. Pain stimuli moves from the periphery via the afferent neurons into and up the spinal cord, through the thalamus and to the cerebral cortex. At this point, we have a conscious perception of the pain and its location. This is the electrical impulse involved in neurotransmission of pain.

Theoretically, nociceptor-driven pain would be abolished with tissue healing, resulting in a pain-free state. However, in chronic pain this does not occur. The linear relationship between the pain experience and nociception is either absent or inappropriate. Also, in FMS there seem to be qualitative differences which point to an impaired processing of sensory information, in this case, pain. The exact mechanism of this dysfunction is not known, but it is theorized that the mechanoreceptors at the pain site either become sensitized or the afferent nerve transmission reaction malfunctions. At the spinal cord level, changes may occur in the processing of pain which also contribute to these differences.[69] It has also been observed in women with FMS that serum nociceptin (a chemical that acts to control pain transmission) concentrations are lower than in controls, with significant differences in this concentration during the luteal phase of the menstrual cycle. It is speculated that this is related to stress and gonadotropin hormones.[72]

73% of FMS patients whose trapezius muscles were biopsied exhibited muscle fibers with a "moth eaten" appearance.

Hyperexcitability of the nociceptive system has been reported in fibromyalgia.[38] In animal studies, repetitious stimulation of a peripheral nerve will result in magnified electrical responses in the dorsal horn neurons of the spinal column. These neurons usually do not transmit pain stimulus. This is known as augmented sensory processing and is referred to as nonnociceptive pain (NNP). Characteristic clinical features of NNP include pain perception disproportionate to tissue pathology. Painful stimuli is interpreted in proportionately greater intensity than should be expected. Also, non-painful stimuli can result in pain. Chronic pain mediated through these NNP receptors can alter the central nervous system. These alterations can be permanent.[69]

Generally, chemicals involved in pain transmission include the excitatory amino acids, neuropeptides, biogenic amines, prostaglandins, mineral ions, nitrous oxide and endogenous opioids, and others.[67] These chemicals can be nociceptive or antinociceptive, which means they can inhibit or decrease the magnitude of the pain transmission signal. Antinociceptive chemicals are usually inhibitory neurotransmitters, such as serotonin, norepinephrine and endogenous opioids. Nociceptive chemicals are usually excitatory neurotransmitters which include substance P, CRH and ACTH.[30]

The role of the neurotransmitters serotonin, norepinephrine and dopamine have been identified in reference to pain stimulus in FMS patients. While studies have shown 5-HTP and various beneficial neuropeptides are not produced in the muscle tissue of FMS[66], metabolites of these neurotransmitters are depressed in the cerebrospinal fluid. This may be suggestive of a low turnover rate and/or a metabolic defect that occurs at a neuroregulatory level.[62]

Other research supporting the idea of a central mechanism stimulating the unique pain reception in FMS includes findings involving the neuropeptides, nerve growth factor (NGF) and substance P (SP).[30,63,65] NGF is necessary for the survival of sympathetic and sensory neurons. NGF normally originates in areas where there is tissue injury and inflammation; it is thought to play a role in modulating inflammation, immune responses and hyperalgesia in adults.[63,64]

Substance P modulates or stimulates cell activity of different types of cells and mediates pain transmission.[71] Found in the brain, intestines and spinal ganglia, it induces vasodilation and salivation, increases capillary permeability and increases smooth muscle tone. SP "alerts" spinal cord neurons to nociceptive signals coming from the periphery, thereby encouraging the transmission of the pain signal.[30,33] SP decreases the synaptic threshold, which allows easier activation of normally silent interspinal synapses and sensitization of second order spinal neurons.[69,70] NGF is thought to facilitate the growth of SP-containing neurons. This may be a mechanism that affects pain transmission. Elevations of NGF and SP in cerebrospinal fluid would indicate an origination of NGF in areas of the central nervous system.[63] Increased cerebrospinal fluid NGF has not been found in patients with painful conditions exclusive of FMS, but has been found to be elevated in patients with multiple sclerosis and brain injury. These results are interesting considering there has been no evidence of inflammatory pathology in FMS. The cause of the increased NGF remains undetermined but it is speculated that it may be a contributing factor or an underlying cause of the SP elevation. Serum SP levels should not correlate to cerebrospinal levels, as enzymes within the serum degrade SP and other neuropeptides. Thus, tissues with any type of neurogenic inflammation would result in decreased levels of these enzymes and a corresponding elevation of SP in those tissues.[30]

SP release is regulated by a feedback mechanism. Increased levels of SP in the brain increases serotonin levels in the spinal cord, which decreases SP release in the spinal cord.[33] This identifies another role of serotonin within the body and the interrelatedness of all the abnormal findings in FMS. Afferent nerve fibers release SP and it can spread into the extracellular space and into the cerebrospinal fluid. If N methyl D aspartate (NMDA) increases, so will release of SP.[69] Tissue hypoxia may again be relevant in the increased SP levels. There are other neuropeptides involved in the serotonin pathway and cerebrospinal levels, which include calcitonin gene-related peptide (CGRP) and hydroxyindoleacetic acid (5-HIAA) and these correlate with pain threshold.[30,33]

Homocysteine levels have also been found to be elevated in the cerebrospinal fluid in FMS and directly correlate to fatigueability. Cerebrospinal fluid B12 was low. Serum homocysteine and B12 levels did not correspond with these abnormalities, suggesting it is limited to the central nervous system. Folate, B1, B2, B6, B12 and riboflavin are necessary for homocysteine metabolism. **B12 is the only factor found to be abnormal in FMS patients**. A possible explanation is that there is a diminished transport of B12 from the serum into the central nervous system, leading to a cerebral B12 deficiency. This may lead to the reduction in the remethylation pathway of homocysteine.[90]

In the initial stages of FMS, the strong potential for **elevated cortisol levels can lead to demineralization within the body**. FMS patients have also been found to have **low free and total calcium levels**.[39] This could also be due to thyroid abnormalities in relation to parathyroid (PTH) hormonal secretion. FMS patients have been shown to have normal PTH levels. Abnormalities in vitamin D metabolism may also contribute to hypocalcemia. Symptoms of hypocalcemia include muscle weakness, cold hands and feet, paresthesias, nervous system excitability and pain aggravation.[38]

The impaired stress response also leads to exhaustion of the autonomic nervous system, which affects muscle tone, vasoconstriction responses, skin conductance and may be responsible for the associated syndromes found with FMS.[30] A chronic pain state is stressful and persistent stress can alter neuroendocrine rhythms and patterns, which has been observed in FMS. All of these abnormalities or irregularities are consistent with pain amplification syndrome. The psychological and neurobiological evidence pointing to the blunted HPA axis function, alterations in the sympathetic nervous system, other stress response axes, and alterations in pain regulatory mechanisms are congruent with the pain and fatigue associated with FMS.[68]

Diagnosing Fibromyalgia Syndrome

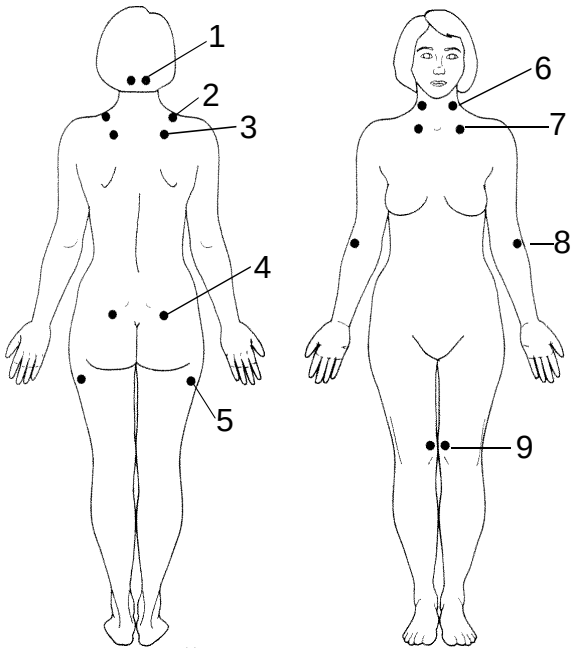
As previously mentioned, there are no diagnostic lab tests or x-rays for defining or diagnosing FMS. Diagnostic "fine points" were defined in 1979 by the American College of Rheumatology. The World Health Organization added their list of symptoms to the syndrome as well.[50] Diagnosis of FMS should be made using the following criteria:

- Non-refreshing sleep
- Generalized morning stiffness
- Persistent fatigue
- Unexplained widespread pain or aching
- Multiple tender points

Other symptoms that may be included: headaches, dysmenorrhea, cold sensitivity, atypical patterns of numbness and tingling, restless legs, Raynaud's phenomenon, irritable bladder, complaints of feeling weak and exercise intolerance.

A history of high stress and a life history of toxicity exposures are other factors that should be considered.

Eighteen tender points that have been specified in the diagnosis of FMS. For a strong diagnosis to be made, at least eleven of those must be present upon examination. Tender points must be present in all four quadrants of the body and the occurring pain must be widespread, constant and have must occurred for at least three consecutive months.



From Fibromyalgia & Chronic Myofascial Pain Syndrome*, Devin Starlanyl, MD and Mary Ellen Copeland, MS, MA*

The location of the tender points are bilateral:

- On the back –
  1. In the occipital region (near the atlas)
  2. Along the shoulders, almost halfway between the neck and shoulder
  3. Diagonally and inward, three finger widths from the last points, near the point of the scapula
  4. Approximately where the sacroiliac joints are located
  5. Posterior to the trochanteric prominence
- On the front –
  6. On the neck, between C5-C7
  7. Still on the neck, just above the clavicle, about four finger widths down from the last point
  8. On the radius, about three finger widths just below the elbow joint
  9. Medially and just above the knee joint, approximately at the medial epicondyle

Gastrointestinal Disorders

Irritable bowel syndrome (IBS) is considered the most common gastrointestinal disorder, accounting for 50% of all patients with gastrointestinal complaints.[76] Symptoms of IBS include diarrhea alternating with constipation, abdominal pain with defecation, flatus, abdominal distention and excessive fecal mucus. These symptoms are usually exacerbated with stress.

It is estimated that as many as **50% of FMS patients suffer from functional dyspepsia and 70% of FMS patients have IBS**.[73,74] Conversely, 28-65% of patients with IBS are believed to have undiagnosed FMS.[73,78] Epidemiological studies confirm that functional gastrointestinal disorders commonly overlap with FMS.[74] 30% of patients with inflammatory bowel disease, 19% with ulcerative colitis and 49% with Crohn's disease have FMS.[75]

Other complaints of bowel dysfunction in cases of FMS include normal alternating with irregular pattern (81%), diarrhea alternating with constipation (63%), flatus (59%), nausea (21%), diarrhea (9%), constipation (12%) and frequent abdominal pain (64%). While FMS patients are not normally diagnosed with IBS, up to 60% may complain of bowel dysfunction similar to that in IBS.[76]

IBS symptomatology in FMS patients may be due in part to alterations of pain sensitivity threshold to stimuli. This leads to distressed bowel function.[76] It has also been speculated that these alterations lead to a perception of altered bowel function.[77] Anxiety, inadequate stress response and sleep disturbance are prevalent in both IBS and FMS. A prolonged stress response causes **increased cortisol levels over a prolonged period of time**, which leads to thinning of the intestinal mucosa and diminished protein synthesis.[126]

IBS patients undergoing colonoscopy with bowel distention have been noted to have muscular pain in sites similar to the FMS tender points.[78] All these similarities indicate that a **high fiber diet may be of benefit in FMS**. Furthermore, many IBS treatments may be effective in FMS as well. Being aware of the similarities may lead to recognition of FMS in patients with gastrointestinal disorders, preventing misdiagnosis and ensuring appropriate treatment.

Sleep Disturbances

As previously mentioned, serotonin and GH deficiencies are generally present in FMS. These factors alone can account for sleep disturbance. **Insomnia, early morning awakenings, unrefreshing sleep and awaking in the middle of the night** are all common FMS-related complaints. In addition, some may experience primary sleep disorders, including sleep apnea.

In sleep studies, normal controls exhibited an alpha-delta sleep anomaly if sleep-deprived or if deep pain was induced during the sleep cycle. This same anomaly was seen in FMS patients. The anomaly manifests itself as an increase in stage 1 sleep, a decrease in delta sleep and an increased number of arousals.[79] During the sleep cycle, the alpha-delta ratio progressively increases. Patients with FMS also have an increased incidence of alpha non-rapid eye movement sleep.[83] These alterations in the sleep pattern have been found to **correlate with increased pain sensitivity, lowered pain thresholds, decreased levels of IGF-1, increased fatigue, overall discomfort and inflammatory flare responses** in the skin.[80,81,82]

Other studies show a **high occurrence of periodic breathing and of sleep apnea** among FMS patients. Sleep apnea occurs in only approximately 2% of the women with FMS, and in **44% of the men who have FMS**.[84] The extent of periodic breathing correlates with transfer factor of the lung for carbon monoxide and carbon dioxide tension in arterial blood.[85] Thus, sleep apnea and periodic breathing interfere with oxygenation of the cells and can lead to hypoxia.

Myofascial Pain Syndrome

Many physicians lump this disorder together with FMS. In reality, they are different syndromes. As discussed, FMS occurs primarily in women but myofascial pain syndrome (MPS) occurs primarily in men.[50] This article has made it very clear that FMS is a biochemical disorder. Currently, MPS is considered primarily a neuromuscular condition. However, many of the same responses and chemicals are involved in both FMS and MPS, and the two conditions may overlap. MPS is **characterized by fascial trigger points, muscle spasticity interfering with the flow of liquids in the body, possible bladder irritability, sinus passages constricting and contributing to a chronic runny nose, and head and neck movement becoming difficult**. Dizziness associated with changes in body position is very common.[86]

Other

Other conditions that may coincide with FMS are:

- **Allergies** – Tests indicate a high incidence of allergies in FMS in comparison to controls.[87]
- **Anxiety and depression** – In comparing FMS with other rheumatologic patients with pain, those with FMS scored significantly higher on the Melancholia Scale, the Depression Scale and the Anxiety Scale.[88]

- **Multiple Chemical Sensitivity** – 20-47% of FMS and/or CFS patients also have severe chemical intolerance.[89] It is thought that the same neurohormonal irregularities and dysfunctions of the regulatory pathways that occur in FMS contribute to the development of chemical intolerance, particularly in FMS. Holistic practitioners have noted many FMS patients report an exacerbation of symptoms after exposure to such things as perfumes, solvent fumes, cigarette smoke and pollution.[126]
- **Cardiac abnormalities** – FMS patients often report **irregular heartbeats** and are often diagnosed with murmurs and/or mitral valve prolapse. Phosphate, free radical activity and tissue hypoxia can all explain the occurrence of a murmur.[53]
- FMS patients have also reported **increased functional impairment, psychological distress and musculoskeletal symptoms** related to weather changes. Beliefs about the weather seem to affect perception of symptoms.[91]
- **Candida** – Many patients with CFS and/or FMS have been found to have candida overgrowth. Candida can also cause symptomatology such as allergy, digestive disturbances, fatigue and cognitive impairment.[95]

Current Medical Interventions

Gentle aerobic exercise, a consistent bedtime, a consistent amount of sleep, and medications (primarily antidepressants) are the current approach.

Prescription Medications

- **Analgesics/NSAIDs** – A wide array of medications are used, including acetaminophen, ibuprofen, aspirin, propoxyphene, codeine, rofecoxib, various other non-steroidal anti-inflammatories and tramadol. Most of these, particularly the NSAIDs, are only temporarily effective in blocking FMS pain.[5] In addition, they alter the permeability of the GI lining and lead to the development of leaky gut syndrome. These medications also destroy much of the healthy bacterial flora in the gastrointestinal system.

  Many of these drugs are **demanding on the liver**, some of the analgesics **affect the central nervous system** and may be abused. Some can also **lower seizure threshold and cause constipation**. Any medication that is salicylate-based can **exacerbate pain** by inhibiting the excretion of phosphate and uric acid.[53]

- **COX-2 Inhibitors** – CyclooxygenaseÝ prostaglandin synthesis. Another new player in the anti-inflammatory regimen are the COX-2 inhibitors. This new introduction is bringing some temporary relief of pain in FMS but still does not focus on the true cause of the pain. It is only approved for acute pain, osteoarthritis and dysmennorhea.
- **Tricyclic antidepressants** – Some of the more commonly prescribed are amitriptyline and nortriptyline and trazodone. While studies show short-term improvement in sleep pattern and tender points, long-term efficacy has not been determined.[92,93,94] In addition, there are side effects which some people find intolerable. These drugs **contribute to leaky gut syndrome** and interfere with the HPA axis, which in turn **interferes with immune function**.[53]
- **Serotonin Reuptake Inhibitors (SSRIs)** – The theory is that by increasing serotonin levels in the brain, sleep will improve. Short-term improvement is reported but there are **no long-term studies on efficacy**.
- **Benzodiazepines** – The most commonly prescribed is alprazolam. Side effects such as **drowsiness, mental impairment and possible addiction** may have a detrimental effect on quality of life and functionability.
- **Muscle relaxants** – Along with the benzodiazepines, cyclobenzaprine is the most commonly prescribed. If cyclobenzaprine or amitriptyline is ineffective, the next option is usually orphenidrine. **Potential side effects** may make these poor treatment choices.
- **Fluconazole** is used if fungal infection is suspected. However, be aware that this medication penetrates all the body's tissues, including the central nervous system.
- **Potaba** may be used to decrease fibrotic tissue and it is recommended in cases of stubborn cases of MPS.[86]
- **Prednisone** has also been used but studies indicate there is no improvement with this drug.[96]

With all prescription medications, potential exists for interference in biochemical associations within the body. There is always the possibility of unpleasant side effects. Many drugs, whether prescription or non-prescription, can **alter bowel terrain**, further contributing to the complications of FMS. Furthermore, **long-term efficacy has not been proven in most cases**. The only certainty is that these drugs are unable to bring sustained symptomatic relief or help in disrupting the disease process.

The Holistic Approach

Because traditional medicine offers very little in the way of true long-term relief to FMS sufferers, many seek out complementary treatment. **44% of FMS sufferers have been reported to use vitamins**, 25% exercise and 23% turn to spirituality/praying. Reflexology, biofeedback, acupuncture, TENS units and ultrasound are used infrequently. The more severe the pain and/or the disability, the more likely a person is to seek out complementary therapies. Individuals age 47 and under are more likely to use complementary therapies than middle aged or senior citizens. Reports indicate that up to **90% of patients with FMS use at least one complementary therapy**.[113] A study by Mengshoel, et. al.[98] found that regular practice of relaxation techniques and dietary changes offer some reduction in pain.

It is important to identify what a patient most wants to accomplish and what symptoms concern them most. While a holistic or integrative practitioner will want to look at the overall issues and try to get to the root of the imbalances, one must often first help the patient feel more comfortable and relieve some of the pain or depression in order to ensure compliance with a total treatment program. **Only a holistic program offers the potential of effective management and allows for improved function**. Therefore, a **thorough and complete evaluation** of symptoms, complaints, history and goals is essential for success. The overall focus is on providing the body what it needs to normalize the biochemical abnormalities.

Nutrition

Diet

A high nutrient, high protein diet is important. Carbohydrates should be complex. Foods that are anti-nutrients (they either deprive the body or compete for nutrients), should be eliminated. Anti-nutrients include sugar, white flour, processed foods, alcohol and caffeine. In addition, many of these foods place stress on the adrenal glands and the liver. Even nutritionally sound foods can undermine nutrient uptake if the patient is allergic to them.[50,95]

Some health care practitioners recommend diets that are almost equal ratios of calories from protein/fats/ carbohydrates.[50] This balance is important in regard to the hormonal responses that occur from eating.[50] In addition, many individuals with FMS will benefit from some type of **glycemic modification diet**. However, one must keep in mind that different biochemistries, based on many factors including ethnicity, blood type, food allergies, other health conditions and personal tastes will influence what balance and what type foods are best for an individual.

Many individuals will do better by grazing throughout the day on beneficial foods or at least eating four to five small meals instead of two or three large meals. In order to function properly, the body must be nourished with proper foods in the appropriate amounts and combinations. It is also important to take time to eat slowly and chew the food thoroughly. While eating, one's focus should be on the food and the process of eating, not on the TV, the newspaper or some other activity.

Reports indicate that up to 90% of patients with FMS use at least one complementary therapy.

Identifying and eliminating any underlying food allergies will be of great benefit. The most common food sensitivities are dairy, caffeine, yeast, citrus, wheat and corn. Some food additives like **MSG, sodium nitrates and tyramine are also problematic**.[50] Also, foods in the nightshade family can create problems for some people because they contain solanine, which interferes with muscle enzymes and can cause pain and discomfort. Foods in the nightshade family include eggplant, white potatoes, green peppers, tomatoes and okra. Most squashes are a relative of the nightshade family and, while usually well tolerated, should be limited if pain aggravation is noted.

It is important to alter the foods one eats on a regular basis. This provides a broader range of nutrients and diminishes the potential for developing food sensitivities. One food rotation study[100] has shown a **42% decrease in symptoms in FMS patients**. In fact, many were able to significantly reduce their prescribed medications. Foods reported to cause the greatest aggravation were alcohol, coffee, sweets, gluten, dairy and some meats.

Pork should be avoided because it is highly inflammatory. Pork can be very difficult for some people to digest, and smoked pork products contain high levels of sulfites and nitrates.

When using salt, make sure the flowing agent used during processing is not aluminum, another metal or another potentially problematic additive. Sea salt is usually the best choice because it is made with a minimum of processing and contains a variety of health essential minerals.

Finally, large quantities of good quality water should be drunk daily. For most people, ½ ounce for every pound of body weight is ideal. Water helps the body flush out toxins and keep cells hydrated. This is particularly valuable to FMS patients undergoing detoxification processes.

Supplements
Nearly every vitamin and mineral is needed in FMS cases. It is important to find **combination supplements that work synergistically** so patients do not get overwhelmed with products. While there is a wide array of choices, some basics will be helpful to everyone in overall nurturing and balancing of the body.

- **Fiber**: Many patients will benefit from added fiber. Fiber adds bulk to the system to reduce bouts of diarrhea and constipation. Also, fiber helps pull toxins from the system and encourages production of fresh bile. The best choice for overall cleansing of the intestine is a combination of flax seed and psyllium. Bran is also a good choice, but only if sugar or artificial sweeteners have not been added. To avoid the additional burden of pesticides on the liver, fiber should be organic.

- **Omega 3 Fatty Acid**: Omega 3 essential fatty acids may help reduce inflammation and pain in FMS. Flax seed oil is an excellent source. One tablespoonful provides over 7000 mg. of linolenic acid versus 75 to 1000 mg. in the highest quality capsule formulations. Flaxseed oil is generally well tolerated by most people in a dose of 1 to 2 tablespoons daily. It may also be added to food, juices, or used as a breadspread or salad dressing. A good quality flaxseed oil should be packaged in amber glass and be refrigerated upon opening. It should have an antioxidant present (such as vitamin E) to extend shelf life and should be a first press, cold press, low viscosity oil.

- **Probiotic**: A probiotic is needed to help **balance the bowel terrain and diminish gastrointestinal symptoms**. Recent clinical studies have shown that a multi-strain combination is more beneficial than two- or three-strain colonizing probiotics.[137,138] The **optimal probiotic formulation would be a multi-strain** that would provide bacterial coverage from the top to the bottom of the GI tract, containing:
  - *Lactobacillus Acidophilus* - Natural inhabitant of the human mouth, vaginal and intestinal tracts. Reduces lactose intolerance, controls diarrhea and colonization of undesirable bacteria. Reduces cholesterol by converting it to coprostanol, a less soluble substance which is then harmlessly excreted. Has been shown to kill candida yeast. Some strains produce natural antibiotics. L-Acidophilus provides protection for the intestinal wall by enhancing antigen-specific immune defense.
  - *Lactobacillus Brevis* - Natural inhabitant of the human intestinal tract. Found in most fermented foods and has been shown to have inhibitory effects on certain pathogenic bacteria.
  - *Lactobacillus Bulgaricus* - Several strains produce antibiotics, which are bacteriocidal. Produces lactic acid which enhances the acidic environment for other friendly bacteria, especially acidophilus and bifidum. L-Bulgaricus has been shown to be beneficial against intestinal infections and enhances the body's immune response. One of the main Lactobacilli used in the yogurt industry.
  - *Lactobacillus Helveticus* - Normal intestinal inhabitant in humans. Has superior colonization ability with highest growth potential at normal body temperatures.
  - *Lactobacillus Lactis* - Produces large quantity of lactic acid in the intestinal tract, which reduces potential for pathogenic bacterial growth. Forms great bulk due to colonization, thus reducing constipation.
  - *Lactobacillus Plantarum* - inhibits growth of pathogenic bacteria. L. Plantarum is a good colonizer, helps reduce flatulence, and aids in production of carboxylic, acetic, and propionic acids which are bacteriastatic to many pathogens.
  - *Lactobacillus Rhamnosus* - Adheres to the intestinal mucosa. Protects against invasion and activities of harmful microorganisms. Inhibits bacterial and fungal vaginal infections and helps prevent diseases caused by intestinal infection.
  - *Lactobacillus Salivarius* - Has been shown to produce alpha-Galactosidase, which helps reduce flatulence. In addition, L-Salivarius is highly resistant to tetracycline and other types of antibiotic therapy thus reducing antibiotic-induced diarrhea.
  - *Streptococcus Thermophilus* - Has been shown to ferment certain carbohydrates. S-Thermophilus has inhibitory effects on harmful bacteria due to strong colonizing ability. Enhances digestion of milk sugar thus reducing lactose intolerance. Used widely in yogurt industry.
  - *Bifidobacterium Breve* - Excellent colonizing ability. B. Breve are smooth and slippery in colonies, thus reducing constipation and aiding in the healing of inflammatory disorders of the intestinal tract.

- *Bifidobacterium Bifidum* - Very abundant in the colon, lower portion of the small intestine, and vaginal tract. These bacteria decline in number with age and health. B-Bifidum produces a number of specialized acids to prevent colonization of the large intestines by pathogenic bacteria & Candida. Aids nitrogen retention by children. Helps manufacture active B vitamins and detoxification of bile making estrogen recycling more predictable.
- *Bifidobacterium Infantis* - Has been shown to be the main inhabitant of every healthy infant's gastrointestinal tract. It is also found in small amounts in the vaginal tract. B-Infantis functions synergistically with B. Bifidum.
- *Bifidobacterium Longum* - Colonizes with B. Bifidum and B. Infantis and has many similar attributes. Has been shown to prevent potential toxicities from nitrites in the diet.
- *Saccharomyces Boulardii* - Species of beneficial yeast that increases several immune system markers and enhances the activity of beneficial enzymes in the mucosa of the small intestine. Has been shown to be effective in prevention and treatment of traveler's diarrhea. Improves Crohn's disease by aiding in the production of SIGA on the GI wall. S. Boulardii does not have to be alive to promote beneficial effects.

Probiotics in powder or non-heat sealed capsule form avoids the heat and moisture associated with tablets, liquids, or gel caps. Common knowledge also states that a quality probiotic must be refrigerated.[129]

❖ **B Complex**: B vitamins are required for serotonin synthesis as well as other neurological, immunological and metabolic functions. A yeast-free B complex is recommended. The relation of B6 and B12 to FMS has already been discussed. Niacin (B3) can be effective in decreasing musculoskeletal inflammations. Inositol works as a lipotropic.[95] Lecithin serves as a neurotransmitter precursor.[95] B1, B2 and B6 are essential to the electron transport system in the respiratory chain. B1 (thiamine) may support proper oxygen metabolism and symptoms of B1 and B6 deficiencies are very similar to those experienced in FMS.[99,108] The combination of B6, B12 and folic acid also serves to decrease the build-up of homocysteine levels in FMS patients. A good B complex supplement should be dosed no fewer than 2 to 3 times daily.

❖ **Minerals**:

- **Magnesium** has been found to be deficient in FMS, so patients respond favorably to supplementation.[101,102,103,104,105,106] While serum magnesium levels may well be within normal limits, tissue levels can still be low.[101] A study by Eisinger, et.al.[104] showed a significant increase in leucocyte magnesium and slight decrease in erythrocyte magnesium. This abnormality was linked to thiamin metabolism abnormalities. Among its many roles in the body, magnesium is important in opening up the circulation to the muscles, a factor of relevance in FMS.[127]
- If there is a need for magnesium, there is usually a need for additional **calcium** as well. Functional calcium may be low. Muscle aches, pains and spasms are indicators of mineral deficiency. Calcium and magnesium deficiency are widespread problems in the general population, let alone the FMS population. As mentioned previously, calcium and magnesium help to reduce the risk of osteoporosis in the FMS patient.
- Malic **Acid** in conjunction with magnesium have also been used together successfully. Abraham and Flechas[105,107] speculated that due to the increased gluconeogenesis and breakdown of muscle proteins (leading to hypoxia and other factors needed for ATP synthesis), magnesium and malate would be beneficial in supporting ATP synthesis and would thus improve FMS symptoms. Using 300-600 mg. of magnesium and 1200-1400 mg. of malate, patients **reported improvement within the first 48 hours** and this improvement continued even after eight weeks using this combination. Russell, et. al.[106] also reported significant improvement in tender points and pain with similar doses of malic acid and only 50 mg. of magnesium.[95]
- **Sodium** is another mineral that is often deficient in FMS. The combination of calcium, magnesium, sodium and potassium regulate the transport systems of the body and determine what enters and leaves the cells.[127]
- **Manganese** is another important mineral, involved in the HPT axis in regulating metabolism and also in its ability to assist in the repair of connective tissue.[107]
- **Selenium** is necessary for conversion of the thyroid hormone thyroxine into its active constituent triiodothyronine. Many FMS patients also display hypothyroidism.[103] Studies by Reinhard, et.al.[103] and Robinson, et.al.[102] showed significant serum selenium deficiencies in FMS patients. Improvements in muscular pain and spasmotic symptoms

occurred in 50% of the patients given supplementation.

- **Zinc** is utilized in more than 200 enzyme activities in the body. Insufficient levels impair the immune system. Zinc is also important in tissue repair, anti-aging, taste and smell.[130]

❖ **Amino Acids**: Amino acids serve as neurotransmitters, precursors for metabolic activity and as cofactors in detoxification. They are building blocks for every cell in the body. They can improve mood and energy. Many amino acids must be obtained through diet or supplementation. Amino acid supplementation is particularly important in FMS patients who have compromised protein metabolism. Some of the most common amino acids used in FMS therapies include:

- **Methionine**: An essential amino acid that contains a high level of sulfur. Methionine improves skin tone and pliability, protects cells from airborne pollutants and slows the aging process. It is essential for transportation and bioavailability of selenium and zinc. It chelates heavy metals such as cadmium, lead, and mercury, and reduces fatigue.[131]

- **Tyrosine**: Manufactured from phenylalanine, tyrosine is an important precursor of brain neurotransmitters including epinephrine, norepinephrine and dopamine. The value of tyrosine in FMS is tremendous as **patients suffer from potentially severe bouts of depression and "brain fog"**. Tyrosine is also used by the thyroid gland to produce thyroxine, a regulator of growth, metabolic rate, skin, and mental health. Tyrosine may possess the ability to initiate migraine headaches in select individuals at higher doses. Monitoring the patient for these problems allows for better compliance and outcomes in these highly sensitive individuals.[132]

- **Arginine**: FMS patients suffer marked impairment of GH. Arginine in its free form (not bound in food) assists in stimulation of GH. Arginine also increases production of collagen to assist in maintenance of the painful connective tissues observed in FMS. Studies have shown that the demand for arginine increases in the presence of physical and mental stress.[133]

- **Ornithine**: Combined with arginine, ornithine stimulates GH production. Ornithine also improves immune system function and aids in liver function and detoxification.[134]

- **Phenylalanine**: Shown to encourage the beneficial effects of tyrosine as a neurotransmitter precursor and to decrease chronic pain. Phenylalanine has been **clinically proven to reduce depression**. This effect is intensified with additional supplementation of vitamin B6.[135]

- **Taurine**: Taurine is generally found in animal products; thus, vegetarians are more likely to have a deficiency. Along with its ability to prevent arrhythmias and motor tics and twitches, taurine shows stabilizing effects on cell membranes, antioxidant and detoxifying activities in the bile and a calming effect on the central nervous system.[136]

If a patient exhibits gastrointestinal issues, as in many cases with FMS, amino acid transport will be disturbed. Toxicities can also interfere with transport mechanisms.[126]

❖ **5- Hydroxytryptophan** (5-HTP): 5-HTP is a serotonin precursor which improves sleep quality as well as GH precursors in some patients. Several studies have reported significant improvement in FMS with 5-HTP supplementation.[8] 5-hydroxytryptophan is an intermediate metabolite of L-tryptophan, an amino acid involved in the synthesis of serotonin. It has about a 70% oral absorption rate. It easily crosses the blood-brain barrier and is very effective in increasing CNS synthesis of serotonin. It has been shown to be effective in fibromyalgia, binge eating associated with obesity, chronic headaches, insomnia and depression.[36] 5-HTP also seems to be involved in the modulation of microcirculation of the musculature of FMS.[37] Chocolate cravings may be an indicator of a serotonin deficiency.

❖ **Antioxidants:** Antioxidants are beneficial as free radical scavengers and support metabolic function. Vitamin C also helps nourish the adrenal glands, is important in building collagen, and has the subject of many clinical studies that indicate its overall health benefits. Vitamin E is beneficial in tissue inflammation and supports cartilage growth. CoQ10 is an enzyme with antioxidant properties that actually enters the cells and works with the ATP cycle. It can help improve energy in addition to its free radical activity.

- **Pregnenolone**: Pregnenolone increases energy metabolism and can improve memory. Pregnenolone is a precursor to DHEA, which converts into sex hormones and cortisol as needed by the body.[8] Pregnenolone may be beneficial in female FMS patients who have reduced hormone and/or cortisol production. Supplementation with pregnenolone or DHEA should not be undertaken without the benefit of an adrenal stress index or a hormone panel (see section on Laboratory Testing).

- **NADH:** Studies in Europe and at Georgetown University have shown improvement in FMS with the use of NADH (nicotinamide adenine dinucleotide).[6] Supplementation with 10 mg. of NADH daily over a four-week period resulted in markedly positive patient responses in the neurocognitive, psychological and physical levels. NADH is known to trigger energy production by generating ATP (adenosine triphosphate) which stores energy in the cells.[6]

- **SAMe**: Two studies on S-adenosyl-L-methionine (SAMe) report improvement in FMS symptoms. Volkmann, et.al.[110] performed intravenous administration of 600 mg. daily for ten days and reported favorable improvement in pain perception at rest, pain with movement and overall well-being. Minimal improvement was reported in overall fatigue, sleep quality and morning stiffness. No improvement was reported in tender points. Tavoni, et.al.[109] reported an improvement in depression and a decrease in tender points with SAMe administration. This would be consistent with the ability of SAMe to reduce neurotransmitter depression in the brain.

- **Interferon**: Interferon injections have also been used in FMS cases. Although significant improvement was seen in morning stiffness (45%) and physical function, no improvement was noted in tender points.[111] There was a more significant response to the injections among Caucasians than Hispanics. 50 IU daily was adequate for this response.

Herbals

Herbals have a very valuable place in FMS. Many FMS patients seek relief from herbal remedies for symptomatic problems. This approach is well and good, but ultimate relief should be found in combinations of herbals along with other adjunctive recommendations. Some herbal entities that have shown effectiveness include:

- **Ginger**: Antispasmodic and cholagogue, helps settle the GI tract from nausea.
- **Kava Kava**: For nervous anxiety, stress, restlessness, insomnia.
- **Bromelain**: Used in digestion to help break down foods so the body can assimilate nutrients.
- **Barley**: Assists in the digestion of carbohydrates and proteins.
- **Beet Root**: Promotes regeneration of liver cells, greatly assists metabolism of fats.
- **Chelidonium**: Tonifies the liver and gallbladder.
- **Dandelion**: Used for poor digestion and water retention.
- **Milk Thistle**: Used to relieve congestion of the liver, spleen, & kidneys.
- **Echinacea**: Supports immune system, increased production of interferon, an important part of the body's response to infections.
- **Andrographis**: Has anti-inflammatory and anti-spasmodic activity.
- **Para Cress**: Has a significant anti-inflammatory effect.
- Astragalus: Enhances immune function.
- Garlic: Aids in reducing parasites.
- Licorice Root: To support the glandular system.

Homeopathy

Homeopathics have been very effective in alleviating pain and discomfort associated with FMS. Recognized as a viable treatment entity by the FDA, homeopathy has assisted in bringing relief to many difficult diseases such as FMS. One of the most effective has been Rhus Tox at a 30x or 30c potency.[127] A double-blind controlled crossover clinical trial was done in England in the department of rheumatology at St. Bartholomew's Hospital. There was a 25% improvement in tender spots in the patients taking the Rhus Tox.[128]

A high potency combination product will likely produce the best results. In fact, many other homeopathic entities have been used successfully in FMS. They include:

- **Alumina**: For tendency toward weakened muscular states, sluggish functions, heaviness of limbs, numbness and constipation.
- **Argentum Metalicum**: For weak and trembling legs. Rheumatic affections of joints, especially elbow and knee.

- **Berberis Vulgaris**: Used for listlessness, apathy, indifference. Also for rheumatic paralytic pain in shoulders, arms, hands, and fingers, legs and feet.
- **Conium**: For weakness of body and mind, trembling and palpitation.
- **Ferrum Metallicum**: For lumbago, better, slow walking. For pain in hip joint, tibia, soles and heels.
- **Gelsemium Sempervirens**: Used for various degrees of motor paralysis. Also used for dizziness, drowsiness, dullness and trembling.
- **Guaiacum**: For immovable stiffness, forgetfulness.
- **Hydrogen**: For limbs that are hot, very sensitive to touch. For piercing pain, aching shoulders and arms extending to fingers. Also used for stiffness of legs, as well as numbness and tingling.
- **Lachesis Mutus**: Useful for patients who are sad in the morning, and for a sense of restlessness and unease. Also for shortening of tendons.
- **Phosphoricum Acidum**: For nervous exhaustion, weakness, tearing pain in joints, bones, and periosteum.
- **Rhus Toxicodendron**: Affects fibrous tissue—producing pains and stiffness. Also for listlessness and sadness.

Other Interventions

Guaifenesin

Guaifenesin has also been used with some success.[50,127] Dr. Paul St. Amand, an endocrinologist in California and professor at the University of California, Los Angeles, believes FMS patients have a defective kidney enzyme that causes phosphates to be retained and accumulate within the cells. Dr. St. Amand has contended that accumulated phosphates are eliminated by using approximately two months of guaifenesin treatment for every year of accumulation.[127] Symptoms of hypoglycemia and salicylate use may render guaifenesin ineffective. Guiafenesin can also be used homeopathically as Guaiacum, particularly in patients that do not tolerate it well as an herb or synthetically manufactured.

Aromatherapy

Essential oils typically used in pain reduction include **helichrysum and lavender**.[120] When massaged into the skin, helichrysum soothes aches and pains, and relaxes tendons and muscles. Lavender can decrease soreness and sprains. The scent of lavender can promote sleep.

Acupuncture

Several studies have been done using real acupuncture versus sham acupuncture in FMS. Time and again, the real acupuncture has shown significant benefit. Sprott, et.al.[112] reported a reduction in pain levels and number of tender points. Berman, et.al.[113] reported pain relief, increased pain thresholds, decreased morning stiffness and improved overall symptom ratings. 50% of subjects reported satisfactory improvement and 25% **reported almost complete remissions**. Acupuncture also provided longer lasting pain relief than other interventions, both conventional and non-conventional.

Studies involving electroacupuncture studies also reported significant improvement.[114] Optimal results occurred with the use of both low and high frequencies. Low frequencies are associated with the release of endorphins and high frequencies with the release of serotonin.[113]

Auriculotherapy

Auriculotherapy, while not exactly ear acupuncture nor electro-acupuncture has shown to be quite effective in reducing pain sites and to promote the nautral healing process of the body.[140] The greater success would lie in the stimulation of the liver and kidneys to improve the pathways of elimination and detoxification. Auriculotherapy has been shown to be of great benefit in reducing the stress, anxiety, restlessness and insomnia components of Fibromyalgia.

Medicinal and mud baths

Medicinal and mud baths have been found to be effective. Mudpacks were used (in conjunction with antidepressant treatment) to influence the HPA axis.[115] Pain diminished and corresponded with an increase in serum corticoids and beta-endorphin. Treatment with valerian baths decreased the number of tender points, improved sleep and overall well-being. Pine oil baths improved well-being but increased shinbone and right deltoid pain. Plain whirlpool baths decreased pain intensity.[116] Ginger baths can stimulate detoxification through the skin via perspiration.[127]

Other Remedies

Osteopathic manipulation has been beneficial for some patients, improving tender points, range of motion and pain threshold.[117,118]

Exercise

Studies and healthcare practitioners consistently find that those who suffer with FMS derive great benefit from consistent, regular, gentle exercise. Aerobic exercise also provides benefits, as long as it is done in moderation or to tolerance levels. The HPA axis can be positively affected by exercise.[121] ACTH, prolactin and growth hormone serum levels increase with exercise.[119] Patients who engaged in cardiovascular fitness reported significant improvements in pain intensity, total myalgia and tender points. Conversely, patients who engaged in only flexibility exercises reported no such improvements.[122,123] Other studies utilizing aerobics and strength training report similar results with improvement in pain, tender points, sleep energy and even depression.[124,125] Activities such as walking, water aerobics, stationary bicycling and cross-country skiing are often good options for someone with FMS.

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Lab Testing

Laboratory testing is imperative for practitioners to get to the root of each individual's problem. Because the scope of FMS is so broad, a thorough assessment should be done with each patient to identify the most likely area of concern. After a full evaluation is obtained, the following lab tests can be used to identify underlying factors that may be linked to or an aggravator of FMS.

- **Adrenal Stress Index (ASI)** – As previously mentioned, the adrenals play a key role in FMS and should be evaluated. A proper Adrenal Stress test measures:
  - **24-hour cortisol production** at selected time frames corresponding to the body's natural biorhythm. Cortisol has a major affect on our energy maintenance, immune function, hormones and feedback to other organ systems.
  - **DHEA levels** (the building block for other hormones in the body)
  - **SIgA levels** (a measure of proper gut function and determinant of leaky gut syndrome)
  - **Antigliadin** (an indicator of gluten sensitivity). A person with a significant sensitivity to gluten proteins will never feel better until these proteins are removed from the diet because gluten sensitivity can negatively affect all GI absorptive abilities.

  Approximately 90% of all patients will generate abnormal results in at least one of these categories. This is the test of choice in most cases because **poor adrenal health will contribute to poor overall health**.

- **UMM** - Urine mineral metals. The test **determines toxic exposure** to heavy metals and potentially toxic substances. It can determine aluminum toxicity, which is implicated in FMS symptoms. The UMM is a 24-hour urinary catch allowing for accurate daily averaging to assess elemental levels. These levels can assist the practitioner in individualizing patient care.
- **Organic acids** - An organic acids test is an effective measure of metabolic activity, stress, deficiency, and/or dysregulation. The organic acids test is a simple urine test that gives us a clear view of the workings of the various processes and cycles in our daily functions. The lab gives values of efficiency in the following categories: energy production, functional cofactors, detoxification, fatty acid oxidation, and dysbiosis markers.
- **Food Allergy** – More and more information is coming to light regarding the negative effects food allergies have on overall health. With the ability to cause unnecessary cortisol release, toxin production and storage, inflammation and a hyper-reactive stimulation of negative immuno-regulators, food allergies can certainly aggravate an FMS patient's condition. Food allergy testing can be a urine or blood test.

SUMMARY - PROTOCOL

Due to the broad etiology of FMS and the many options for protocols, it is appropriate to outline a basic program to get patients to begin the healing process. Much of the initial program involves **rebuilding the digestive process, alleviating pain, making better dietary choices, identifying adrenal abnormalities and improving mood and outlook for better health**.

The very first step must always be attaining a full and complete health history. This allows us to focus on a patient's specific concerns and problems, lays out a proper plan of attack, and keeps a running log of patient progress. **FMS-specific questionnaires are available** to give practitioners a roadmap to the patients' individual needs.

The next step is to run lab tests based on information attained from the health assessment. **All FMS patients need to run an adrenal evaluation test**.

While waiting for return of results from lab testing, each patient should begin an aggressive "gut program". Digestive enzymes, a hydrochloric acid stimulator, B complex vitamins, herbs for digestive balance, basic amino acids, other basic essential vitamins, probiotics, omega-3 oil and fiber combine to form the "gut program". Attention should be given to finding **combination supplements that reduce the sheer volume of pills** that a patient must consume on a daily basis. While the vitamins, herbs aminos and glandulars can all be combined into an effective single product, the probiotic and omega-3 oils must be taken by themselves.

Attention to diet and exercise are highly valuable in providing quicker and lasting outcomes. An adjunctive homeopathic based on patient specific problems is absolutely necessary to encourage a positive patient outcome. The homeopathic of choice should be a **high-potency (30x or 30c) combination product containing as many of the recommended individual remedies as possible**.

Lastly, using a malic acid and magnesium product can be a very effective analgesic for the FMS patient. The dosing of this product can vary based on daily pain thresholds.

Total care of the FMS patient must be individualized from here. Each patient will progress at different rates and reach certain plateaus over time. A skilled practitioner can overcome the many barriers that a complex disease such as FMS.

FINAL COMMENTS

As we have seen, FMS is a complex disease with many influencing factors. It is no wonder that no two FMS patients exhibit the same symptoms or follow the same pathway. With this in mind, it is perfectly clear that no two patients can be treated successfully with a magic bullet or a "one size fits all" approach. Successful alleviation of FMS requires a thorough "peeled onion" approach to therapy. In other words, a trained practitioner will need to peel back the layers of this disease to slowly uncover the many individual disorders that haunt FMS patients.

Attention to research can help lay out a plan for successful alleviation of FMS, its symptoms, and its underlying causes. As we have seen, this therapy must include attention to the digestive system, the musculoskeletal system, neurotransmitters, and cellular detoxification. Multi-faceted therapies have shown promise where traditional therapies have failed.

A skilled practitioner must also keep in mind that **FMS has significant psychological effects that can inhibit improvements and compliance.** All therapies must incorporate patient support as a stimulus. This support can be found through FMS support groups, the Arthritis Foundation, or good patient contact and supportive therapy. FMS can be beaten with an open mind, a long range nutritional approach, removal of negative influences (both mental and physical), and hope for a pain- and fatigue-free future.

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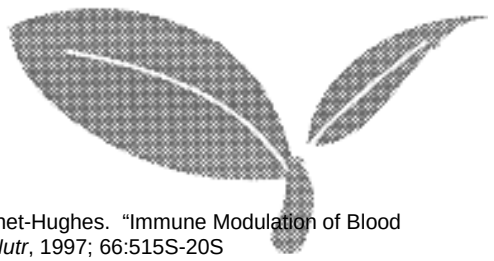

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