Fibromyalgia and the Serotonin Pathway

by John H. Juhl, D.O.

Abstract

Fibromyalgia syndrome is a musculoskeletal pain and fatigue disorder manifested by diffuse myalgia, localized areas of tenderness, fatigue, lowered pain thresholds, and nonrestorative sleep. Evidence from multiple sources support the concept of decreased flux through the serotonin pathway in fibromyalgia patients. Serotonin substrate supplementation, via L-tryptophan or 5-hydroxytryptophan (5-HTP), has been shown to improve symptoms of depression, anxiety, insomnia, and somatic pains in a variety of patient cohorts. Identification of low serum tryptophan and serotonin levels may be a simple way to identify persons who will respond well to this approach.
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Introduction

Fibromyalgia syndrome (FMS) is a musculoskeletal pain and fatigue disorder manifested by diffuse myalgia, localized areas of tenderness, fatigue, lowered pain thresholds, and nonrestorative sleep. Its prevalence has been reported as being 2-6 percent of the general population,[1,2] with about 90 percent of FMS patients being women. Diagnostically, rheumatological criteria requires the presence of 11 or more of 18 specified tenderpoints on physical exam. Although there is no generally-accepted etiology, persons with FMS tend to have a much higher frequency of a group of similar disorders that are identified individually by the person or health care provider, but are often not appreciated as a cluster, the bull's eye of which is FMS. These include chronic headache, temporomandibular joint disorder, mitral valve prolapse, irritable bowel syndrome, dysmenorrhea, interstitial cystitis, vulvodynia, and restless legs syndrome (see Figure 1). A recent prospective seven-year study of 538 persons with a diagnosis of FMS[3] found they averaged 10 outpatient visits per year, and one hospitalization every three years. A recent multi-center study found that 26 percent of FMS patients surveyed were receiving some form of disability payment.[4]

The Serotonin Pathway

Serotonin is one of the major neurotransmitters in the body. It plays a role in sleep, pain thresholds, vascular constriction and dilation, and dynamics of hunger/satiety and libido. It also plays a prominent role in depression, anxiety, and possibly obsessive-compulsive disorders. Its significance in these areas can be appreciated by the phenomenal growth and popularity of drugs like Prozac, which operate as selective serotonin re-uptake inhibitors (SSRIs).

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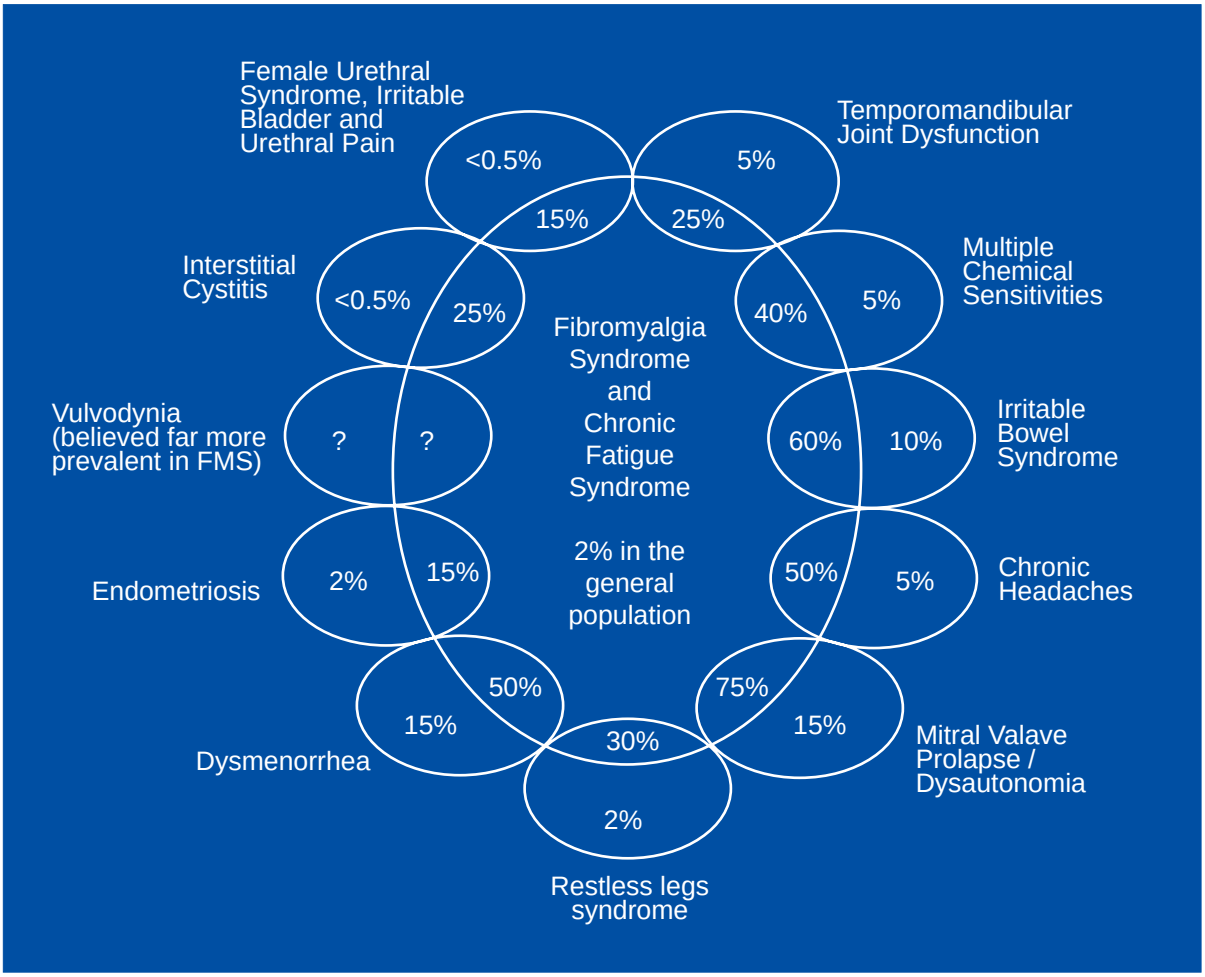
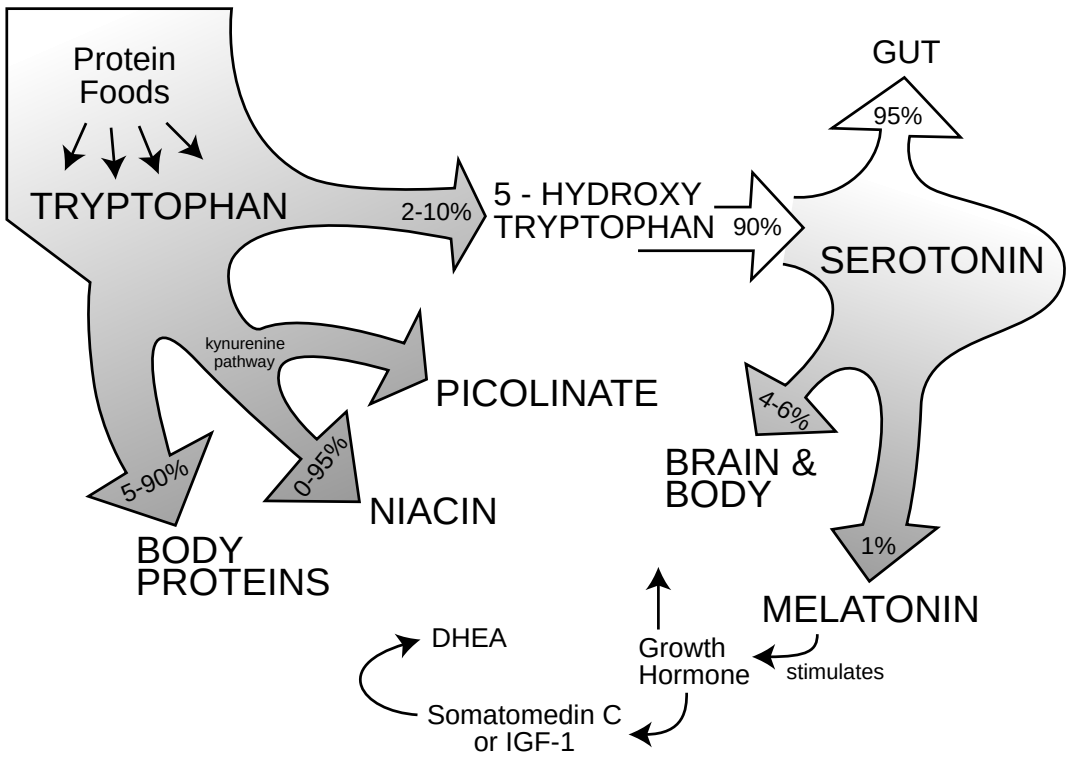
Figure 1. Conditions related to Fibromyalgia Syndrome.



The serotonin pathway begins with L-tryptophan (see Figure 2). Of the eight essential amino acids, tryptophan is the least common, accounting for only about one percent of protein content. After absorption from the gut to the bloodstream, tryptophan is carried by proteins and in free form to peripheral sites, where typically 90 percent is used for protein synthesis, about one percent converted to sero-tonin, and the balance is used to produce niacin. It takes 60 mg of tryptophan to produce 1 mg of niacin, for which the RDA is 15 mg. The enzyme tryptophan pyrrolase (tryptophan 2,3-dioxygenase) is the first enzyme in the conversion to kynurenine, picolinic acid, and niacin, and is inducible by cortisol and tryptophan.[5,6]

In the formation of serotonin, tryptophan is hydroxylated to 5-hydroxy-tryptophan (5-HTP) by tryptophan hydroxylase, which is tetrahydrobiopterin dependent and the rate-limiting step in serotonin production. 5-HTP cannot be degraded to kynurenine, nor can it be borrowed to enhance niacin production or used as a substitute for tryptophan in protein production. 5-HTP is converted to serotonin by an aromatic amino acid decarboxylase enzyme, which is vitamin B6 dependent. Tryptophan is transported across the blood-brain barrier via a transport molecule which also carries leucine, isoleucine, and valine, and prefers leucine. 5-HTP easily crosses the blood-brain barrier and does not utilize this transport mechanism; thus, it does not compete for

Figure 2. Tryptophan metabolism.



passage through the blood-brain barrier with these amino acids.[6]

Serotonin and FMS

In 1989, I.J. Russell found low serum levels of serotonin in a group of FMS patients.[7] A subsequent study by Russell found lower levels of serotonin breakdown metabolites in the cerebrospinal fluid (CSF) of a group of FMS patients, as well as a group of patients with rheumatoid arthritis.[8]

In an extensive review of the neurochemical pathogenesis of FMS[9] and in other studies, both low levels of tryptophan[10] and serotonin[11] in the serum, and low levels of tryptophan and 5-HTP in the CSF were found in FMS patients.[12] Low serum serotonin levels have been found to have an inverse correlation with clinical measures of perceived pain.[13] Studies showing higher levels of metabolites in the kynurenine pathway, which diverts tryptophan away from serotonin production, were found in the CSF of FMS patients.[14] In animal studies[15] serotonin has been shown to down-regulate the nociceptive process in the spinal cord. At least two groups[8,16] have documented low levels of 5-hydroxy indole acetic acid, the final excretion product of serotonin, in the CSF of FMS patients.

High levels of serotonin and its metabolites were found in the hippocampus area of the brain during stage IV sleep in a study of cats by Wilke,[17] suggesting increased synthesis in mammals in the central nervous system during deep sleep. Moldofsky, in one of the early seminal studies of FMS,[18] found a correlation between the nonrestorative sleep reported by most FMS patients and a characteristic alpha-wave intrusion into stages III and IV of deep sleep. Whether this disturbance of sleep architecture is the cause, an effect, or an epiphenomenon of disrupted serotonin metabolism, disturbances in the serotonin pathway seem to be an intrinsic characteristic of

Table 1. Foods high in tryptophan.

Food & Serving	mg/serving.
Spirulina seaweed, (dried 2 oz.)	580
Soy nuts, 1/2 cup	495
Chicken liver, 3 1/2 oz.	332
Pumpkin seeds, 1/2 cup	328
Turkey, 3 1/2 oz.	323
Chicken, 3 1/2 oz.	320
Tofu, 1/2 cup	310
Watermellon seeds, 1/2 cup	222
Almonds, 1/2 cup	204
Peanuts, 1/2 cup	176
Brewers yeast, 1 oz.	150
Cottage cheese, 1/2 cup	173
Milk, 1 cup	113
Yogurt, 1 cup	67

fibromyalgia. These studies support the concept of a decreased flux through the serotonin pathway in FMS patients.

Growth hormone (GH), normally produced by the pituitary during deep sleep, induces the liver to release insulin-like growth factor (IGF-1), which then collaborates in the release of dehydroepiandrosterone (DHEA) from the adrenal glands. Lower levels of IGF-1 have been observed in FMS patients.[19] The relation between melatonin and GH production and release in deep sleep is not fully understood, but it provides a theoretical connection between lower serotonin levels and myalgia through a relative deficit of IGF-1's anabolic (building) effect on muscle tissue. Further downstream, Russell has reported finding lower levels of DHEA sulfate in FMS patients.[9] Known components of the serotonin pathway can be visualized in Figure 2.

The FMS patient's response to these biochemical disequilibriums is an increase in substance P (for pain) in the CSF,[20,21] and probably in the peripheral nerves and muscle tissue. Serotonin is believed to influence pain thresholds by interacting with substance P and potentiating endogenous endorphin effects.[22] Studies in painful diabetic neuropathy have found a high correlation between substance P levels in peripheral nerves and the CSF.[23] Substance P appears to be produced peripherally, then flows to the CNS. To demonstrate this, animal studies have shown that cutting spinal nerves before they enter the spinal cord can decrease the spinal cord content of substance P by 95%,[24] while severing the spinal cord results in accumulation of substance P only at the distal caudal end of the cut.[25]

An attractive thesis is that as various forms of somatic dysfunction accumulate in FMS, substance P generated peripherally in the soma builds up and then moves centrally through the nervous system to produce lowered pain thresholds. Lowered pain thresholds allow more pain to be perceived centrally, causing alpha-wave intrusion into deep sleep and disturbing the concert of reparative processes, forming a positive-feedback loop of dysfunction characterized by decreased flux through the serotonin pathway. How could such a theory be tested, and more importantly would the interventions implied by the thesis improve the symptoms of FMS? The one-disease-one-biochemical-defect-one-drug model has not been shown to be effective in curing FMS, or most chronic conditions. Viewing the syndrome as a circle of interdependent factors would allow simultaneous approaches from a number of different directions.

The musculoskeletal discomfort in FMS is often treated with a variety of physical medicine modalities. This author's experience is with osteopathic treatment, which is based on facilitating the body's ability to heal itself through reduction of somatic dysfunction and by normalizing the neural balance between peripheral structures and the central nervous system. Patients who present with the label of FMS and who normalize solely with osteopathic treatment are more correctly categorized, in this author's opinion, as having

had a form of secondary FMS. However, in many cases of FMS it is not curative, and provides only temporary or partial relief. That alone is not inconsequential; but in an effort to understand the central mechanisms and help FMS patients more, it may be important to check serum tryptophan and serotonin levels. On finding low levels of one or both of these amino acids, substrate supplementation is recommended as a means of increasing the flux through the serotonin pathway.

Tryptophan and Fibromyalgia

In the early 1980s, L-tryptophan was studied and used for a variety of problems ranging from insomnia to depression, usually requiring 3-6 grams a day. Until recently tryptophan has not been available as a supplement or by prescription, having been removed from the market by the FDA after an eruption of side-effects caused by a contaminated batch in 1989. It is currently available by prescription only. In 1981, Van Praag[26] reviewed ten studies published over the prior decade that utilized tryptophan in the treatment of depression, the most common co-morbid condition occurring with fibromyalgia. L-tryptophan was found to be effective in the treatment of depression, and was as effective as imipramine (a tricyclic antidepressant) in a subset of cases. The review did not report any studies where patient selection was made on the basis of low serum tryptophan or serotonin levels.

In a literature review, no studies utilizing tryptophan in the treatment of FMS were found, probably due to its absence from the market during a time FMS research was advancing. There are four not-insurmountable problems in using tryptophan to increase flux through the serotonin pathway: 1) availability, 2) concern about purity, 3) the large dose required, and 4) up-regulation of tryptophan pyrrolase, the degradation enzyme induced by higher concentrations of tryptophan.

The 5-HTP Connection

In the body, 5-HTP is converted directly to serotonin. It is not broken down by tryptophan pyrrolase, and it does not have to compete for transport across the blood-brain barrier. Unlike tryptophan, it is not produced commercially by a fermentation process. Instead, it is extracted from the seeds of *Grifonia simplicifolia*, a plant grown in West Africa. In studies utilizing 5-HTP in the treatment of depression, with dosages ranging from 200 to 3000 mg per day, it was found that, "5-HTP is of therapeutic value, particularly in the serotonin-deficient subgroup of vital depressions."[26]

In a double-blind, placebo-controlled, comparative multicenter trial of 60 patients with depression randomly receiving either fluvoxamine (an SSRI) or 5-HTP orally three times per day for six weeks, outcomes were equivalent for improvements in depressive mood, anxiety, insomnia, and somatic pains. Adverse side-effects, including nausea, were higher in the fluvoxamine group.[27] Patient selection was not based on serum tryptophan or serotonin levels.

Since low serotonin levels have been observed in FMS patients, at least two published studies have utilized 5-HTP in the treatment of primary FMS. In a double-blind, placebo-controlled study, 5-HTP (100 mg three times daily) was given to 50 fibromyalgia patients for 30 days. All clinical parameters studied, including number of tender points, subjective pain severity, morning stiffness, sleep patterns, and anxiety were significantly improved, and only mild and transient side-effects were reported.[28] The same research group later reported on a 90-day open study of 5-HTP, 100 mg three times per day in primary FMS. Significant improvement was noted in anxiety, pain intensity, quality of sleep, fatigue, and the number of tender points.[29]

Fibromyalgia and migraine commonly occur together, and it has been hypothesized

Table 2. Signs and symptoms of serotonin syndrome.

Sign / Symptom	Frequency %
Cognitive-behavorial symptoms	
Confusion / disorientation	51
Agitation / irritability	34
Coma / unresponsiveness	29
Anxiety	15
Autonomic nervous system	
Hyperthermia	45
Diaphoresis	45
Sinus tachycardia	36
Hypertension	35
Dilated pupils	28
Tachypnea	26
Neuromuscular	
Myoclonus	58
Hyperreflexia	52
Muscle rigidity	51
Restlessness / hyperactivity	48
Tremor	43
Ataxia / incoordination	40
Clonus	23

that they share a common etiology, low serotonin levels. In a one-year study, 5-HTP, 400 mg per day, was administered orally to 200 FMS patients who also experienced migraines. At the 12-month assessment, 5-HTP was found to be as effective as tricyclic or monoamine oxidase inhibitor drugs (MAOIs), without the side effects experienced by these drugs. A combination of 5-HTP and the MAOIs (pargyline or phenelzine) was more effective than either substance alone.[30] No studies have been published in which the subset of primary FMS patients with low tryptophan or serotonin levels were selected for a trial of substrate supplementation.

Clinical Findings

Initial results of substrate supplementation in FMS patients in this physician's office have been encouraging. Often in these patients the serum tryptophan level is in the normal range and the serotonin level is low. After careful discussion of the risks, benefits, and alternatives, a trial of 5-HTP is offered, starting with 50-100 mg three times per day. The most common side-effect of 5-HTP is mild nausea, which can be reduced or avoided by taking the supplement with meals. The effective daily dose range appears to be 200-1000 mg. Serum serotonin levels were noted to rise predictably for a given dosage.When both serum tryptophan and serotonin levels are low in these patients, it is recommended to utilize the following nutrients in the treatment plan: vitamin B6 (to increase conversion of 5-HTP to serotonin), niacinamide (to inhibit the need for tryptophan to convert to niacin), and an increased protein intake (emphasizing foods high in tryptophan–see Table 1).

One final non-pharmacological means of stimulating flux through the serotonin pathway may occur by the use of exposure to light at close range in the morning. Persons with seasonal affective disorder (SAD) have been shown to respond to phototherapy in the winter months with improved mood.[31] Rao et al compared the responses of a group of depressed patients without SAD and a group of healthy controls to artificial light at close range for two hours each morning. Both groups' 24-hour serotonin levels increased significantly. The authors did not think their data was strong enough to support a causal relationship between the light exposure and increased serotonin levels, but noted, "If improvement with light therapy is a placebo response, our serotonin data raise the possibility that the placebo response involves increases in serotonergic activity."[32]

The best patient response seen in this office has been an abrupt reduction in myalgia symptoms and a leveling in mood corresponding with a normalized serum serotonin level. After a period of about six months, the

Table 3. Intervention in fibromyalgia.

FIBROMYALGIA	INTERVENTION
I. Nonrestorative sleep	Melatonin, Flexeril, Ambien, 5-HTP
II. Exercise / Breath	1)Yoga 2) Tai Chi 3) Low impact aerobic activities
III. Somatic Dysfunction Temporomandibular Disorder Myofascial Trigger Points	1) Osteopathic treatment 2) Cranial therapy 3) Trigger Point Injections
IV. Low Pain Threshold	1) Tryptophan and Serotonin levels 2) Substrate supplementation with tryptophan or 5-HTP 3) Light therapy
V. Nutrition	Tryptophan, 5-HTP, protein, magnesium, taurine, DHEA, B-complex vitamins, essential fatty acids where indicated.
VI. Information Updates and Lobbying	The Fibromyalgia Network P.O. Box 31750 Tuscon, AZ 85751-1750 (800) 853-2929.

patient elected to reduce 5-HTP medication for financial reasons. His symptom complex did not return and his serotonin level remained normal. He continues to receive osteopathic treatments periodically to reduce musculoskeletal symptoms, and presumably to inhibit the peripheral buildup of substance P.

The fact that women on average have a lower capacity to produce serotonin than men may explain the higher prevalence of FMS in women.[33] Another curious pattern which has emerged in this author's work is that patients on SSRIs (Prozac, Paxil, Zoloft) with lowered pain thresholds also often have low serum serotonin levels. These patients with low serotonin levels on SSRIs were administered low doses of 5-HTP in gradually increasing doses, due to concern that serotonin syndrome may be induced (see Table 2). There are no reported cases to date of serotonin syndrome induced by 5-HTP.

Conclusions

Fibromyalgia is a syndrome, a collection of observed characteristics that reflects a heterogeneity of causes. A large subset of FMS patients have low serotonin levels, but lowered serotonin levels are also found in a number of other chronic pain syndromes. Other possible etiologies for FMS are being investigated.

Substrate supplementation has been shown to improve symptoms of depression, anxiety, insomnia, and somatic pains in a variety of patient cohorts. Identification of low serum tryptophan and serotonin levels may be a simple way to identify persons who will respond well to this approach.

A complementary approach to the treatment of fibromyalgia utilized by this author includes nutritional supplementation, nutritional/pharmacological enhancement of deep-stage sleep, osteopathic treatment of

somatic dysfunction, exercise, and serotonin substrate/receptor modulation where appropriate (see Table 3).

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