

## Nutritional Management of Fibromyalgia

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### Abstract

Fibromyalgia treatment has been a conundrum for clinicians and patients for decades. Understanding of the mechanisms of disease has been limited, and this has led to less than satisfactory options for therapies. Diminished levels of neurotransmitters that are involved in inhibition of pain signals may help to partially explain the symptoms associated with Fibromyalgia. Decreased concentrations of the amino acid precursors to these neurotransmitters suggest that a nutritional deficiency exists and provides potential nutritionally mediated therapeutic targets. Studies have also demonstrated increased oxidative stress and lower antioxidant levels in fibromyalgia patients. Further understanding of the causes of these deficiencies, be it malabsorption, increased turnover or impaired conversion will help to better define nutritionally based treatments.

headaches, non cardiac chest pain, Irritable Bladder and Interstitial Cystitis. Anxiety and Panic Disorders are common in patients with fibromyalgia and contrary to popular belief; depression is less common than originally thought.

The diagnostic criteria for fibromyalgia which were proposed in 2010 [2] include the following:

Widespread pain index (WPI)>7 and symptom severity (SS) scale score>5 or WPI 3-6 and SS scale score>9. Symptoms have been present at a similar level for at least three months. The patient does not have a disorder that would otherwise explain the pain.

Studies have suggested abnormalities in nervous system function are common among the fibromyalgia population such as interpretation of sensation which leads to central amplification of pain signals (i.e. normal sensation feeling like pain or mild pain feeling like severe pain). Also, relative sympathetic hyperreactivity caused predominately by decreased parasympathetic autonomic nervous system function is seen in this population, specifically lack of parasympathetic activation at night [3].

Studies have suggested that the reduction in antioxidant capacity correlates with FM symptoms. Increased oxidative stress has been noted in fibromyalgia patients as well as reduced total antioxidant capacity [4,5]. Serum glutathione levels appear to be reduced in fibromyalgia patients. It has been postulated that mitochondrial dysfunction may play a role in the increased oxidative stress seen in this population.

Effective treatment options for people with fibromyalgia have been limited. Multimodality programs involving physical and occupational therapy, sleep and dietary counseling, aquatic therapy and psychology to deal with secondary triggers can be effective but few good programs exist and it can be expensive and time consuming [6,7]. Medications used to treat widespread pain and sleep related to fibromyalgia have met with mixed results at best. To date, there has been no effective medication to treat "fibro fog" which impairs the ability to focus and concentrate on daily tasks. Common choices for treatment consist of the following.

**Keywords:** Amino acids; Fibromyalgia; Medical foods

### Introduction

Fibromyalgia syndrome affects 2-3% of the world's population and is characterized by widespread pain, concomitantly with fatigue and non restorative sleep [1]. Patients typically complain of pain over much of their body, but almost always in the back and neck region. The pain is present most if not all of the time. The sleep disturbance in fibromyalgia is characterized by having the ability to fall asleep, but then waking up several times per night and having difficulty falling back asleep. Fibromyalgia patients have decreased Stage III/IV and REM sleep and wake up not feeling refreshed. Fibromyalgia predominately affects women and can strike at any age and can lead to significant disability.

People with fibromyalgia commonly experience "fibro fog" or "brain fog," which can impair immediate and short term memory. Other common symptoms include Irritable Bowel Syndrome, Temporal Mandibular Joint dysfunction, chronic

## Analgesics

Over the counter pain relievers are the first line of treatment and a prescription pain reliever may be used for more severe cases. Non steroidal anti-inflammatory drugs (NSAIDs) are minimally effective and can cause gastrointestinal side effects, especially in the patients with irritable bowel. Narcotics are utilized but typically are avoided due to the high risk of dependence [8].

## Antidepressants

Tricyclic antidepressants such as amitriptyline and trazodone have shown some mild benefit, usually by improving sleep. Dual serotonin/norepinephrine reuptake inhibitors such as duloxetine and milnacipran may help to alleviate pain and fatigue associated with fibromyalgia in a subsegment of patients by increasing these neurotransmitters both centrally and on inhibitory pain pathways. Selective serotonin reuptake inhibitors, despite evidence of diminished levels of serotonin in fibromyalgia patients have proven to be minimally effective at best [9].

## Anti-epileptics

Pregabalin and gabapentin may provide pain relief in some patients by reducing the release of excitatory neurotransmitters such as glutamate by blocking the alpha-2 delta subunit of the voltage gated calcium channels in the central nervous system [10]. Night time only dosing can potentially reduce some of the daytime somnolence seen with pregabalin [11].

## Stimulants

Modafinil and armodafinil have been used to treat the fatigue associated with fibromyalgia, but studies are limited and worsening sleep can be an unwanted side effect.

## Benzodiazepines and Hypnotics

Many of these have been used to treat the sleep deficiencies associated with fibromyalgia, but they do not restore deep or REM sleep and are addictive.

Although a definitive cause of fibromyalgia has not been determined, research has focused on a dysfunction of pain processing mechanism leading to a heightened sensitization to pain [12]. Pain perception is the result of a bidirectional process of ascending and descending pathways.

In patients with fibromyalgia both the ascending and descending pain pathways operate abnormally resulting in amplification of pain signals. Pain signals are transmitted via neurotransmitters in the central nervous system. Researchers have found neurochemical imbalances are associated with amplified pain perception characterized by allodynia (a heightened sensitivity to stimuli that are not normally painful) and hyperalgesia (an increased response to painful stimuli).

The levels of neurotransmitters in fibromyalgia patients that facilitate pain transmission are elevated while levels of neurotransmitters that are known to inhibit pain transmission are decreased [13].

The multisystem symptoms that are present in fibromyalgia patients point to dysfunction of the autonomic nervous system. Nocturnal sympathetic hyperactivity may induce the characteristic sleep fragmentation present in fibromyalgia. Fatigue can be accounted for by a deranged sympathetic response to stress. The hallmark of fibromyalgia, widespread pain, may also be due to sympathetic dysfunction. Heart Rate Variability (HRV) analysis has been used to test the theory of autonomic dysfunction in fibromyalgia.

Imbalance of neurotransmitters in patients with fibromyalgia has been well documented by researchers. Research established that patients with fibromyalgia have significantly lower plasma concentrations of the amino acids tryptophan, histidine and serine than normal controls. It is theorized that the relative deficiency in these amino acids play a role in the pathophysiology of fibromyalgia [14]. Neurotransmitters that generally act to increase ascending input, including substance P, glutamate and brain-derived neurotrophic factor are present in higher levels in the cerebral spinal fluid of fibromyalgia patients than healthy controls. Conversely, the activity of descending, antinociceptive pathways is also decreased as evidenced by lower cerebral spinal fluid levels of metabolites of serotonin, norepinephrine and dopamine [15,16].

Many of the neurotransmitters that influence pain perception also influence mood, energy and sleep. Imbalances of these key neurotransmitters in different areas of the brain may also explain the mood disorders, sleep dysfunction and fatigue frequently associated with fibromyalgia [17,18].

Neurotransmitters are the key communicators within the central nervous system. Malfunction of neurotransmission occurs when levels of a neurotransmitter are too high or too low. Abnormal levels of the following neurotransmitters have been demonstrated in patients with fibromyalgia:

Serotonin – effects the sleep cycle, pain processing, appetite and mood

Norepinephrine – effects alertness and memory

Gamma-aminobutyric acid (GABA) – effects sleep and anxiety

Glutamate – stimulates the mind

Although autonomic nervous system dysfunction has been frequently documented in fibromyalgia patients, there is no single test for assessing autonomic function. Investigators have used a variety of techniques to examine the function of the autonomic nervous system including biochemical markers such as catecholamine concentration, norepinephrine levels and heart rate variability analysis [14-16]. As previously discussed, abnormal levels of key neurotransmitters are consistently present in fibromyalgia patients.

Heart rate variability analysis is one tool that has been used to assess autonomic nervous system function in fibromyalgia patients [19]. It has been observed that these patients have changes consistent with relentless hyperactivity of their sympathetic nervous system and suppression of nighttime parasympathetic activity. Such dysfunction can be characterized as a sympathetic nervous system that is continuously hyperactive but hypo-reactive to stress due to an overworked sympathetic nervous system that has become exhausted [20]. Van Denderen and associates attempted to quantify autonomic function during exercise in patients with fibromyalgia. The researchers noted that the patients with fibromyalgia had lower heart rates and lower levels of circulating catecholamines at the same workload compared to healthy controls [21]. The resulting sympathetic hypo-reactivity may be the cause for the excessive fatigue and mental “fog” that affects many patients while the hyperactivity is associated with sleep disturbances.

Fibromyalgia can be considered a disease of the nervous system having a profound effect on autonomic nervous system function. Impaired autonomic nervous system function can alter amino acid catabolism and neurotransmitter production yielding specific dietary deficiencies that cannot be addressed through altering the diet alone.

The dietary deficiencies present in fibromyalgia are supported by a large body of peer-reviewed data which supports the basis for increased requirements of specific amino acids in conditions which are impacted by neurotransmitter imbalances [22-24]. Patients with fibromyalgia show decreased blood levels of certain amino acids despite maintaining a normal protein intake indicating that the need for these amino acids are selectively increased in fibromyalgia patients. This deficiency has been documented in fibromyalgia patients by clinical studies which reported statistically significant improvements in musculoskeletal pain, fatigue and memory in patients after consuming 1000-2000 g/d of acetyl-L-carnitine over an 8-24 week period [25,26]. Improvements in functional status have also been observed following administration of supplemental amounts of acetyl-L-carnitine in senior adults (>70) with physical and mental fatigue. In a double-blind, placebo-controlled trial of 102 patients diagnosed with fibromyalgia, those who received supplemental acetyl-L-carnitine for a 10 week period had statistically fewer tender points and lower self-assessed myalgic scores [25].

Data such as this supports the use of amino acid based medical foods to manage the distinct nutritional requirements of fibromyalgia patients. These specialized dietary management products are designed to replenish amino acid reserves and restore the depleted neurotransmitters that are required by patients with fibromyalgia to restore balance to a dysfunctional autonomic nervous system.

Technology which facilitates the uptake and utilization of neurotransmitter precursors while preventing attenuation of the precursor response can help to improve symptomatology. This technology allows for the use of very small amounts of amino acid precursors while improving metabolic efficiency.

The small amount of amino acid precursors that are used makes dosing very feasible for the patient.

It is unknown whether or not the abnormal neurotransmitter levels are due to inadequate supplies of amino acids, malabsorption or a disruption in metabolism. Further study is needed for the development of effective treatment and possible prevention of fibromyalgia.

The suggestion that increased oxidative stress can play a role in fibromyalgia has led to the examination of antioxidant vitamins and supplements as potential treatment options. Unfortunately, most studies to date have not supported their use with the possible exception of CoQ 10. Several small trials have shown that CoQ 10 levels are decreased in fibromyalgia and that supplementation can help with symptoms, including pain and fatigue [27,28]. Studies looking at other supplements including Vitamin A, Vitamin C, Vitamin E, Magnesium and Meyer’s Cocktail have not shown to be of benefit [29,30].

## Discussion

Restoring homeostasis of the neurotransmitter levels in fibromyalgia patients may be the first step in effective treatment. Addressing the dietary deficiencies that are present in fibromyalgia rather than treating symptoms alone appears to be efficacious.

A combination approach with the use of medical foods to treat the multiple symptoms of fibromyalgia including widespread pain, sleep disturbances and “fibro fog” has proven to be a safe and effective treatment for fibromyalgia patients. Patients with sleep disorders demonstrate a nutritional deficiency of tryptophan, choline and GABA. Fibromyalgia patients also have reduced blood levels of serotonin and 5-hydroxytryptophan.

A double-blind, randomized trial compared an amino acid based medical food with trazodone to study sleep latency and parasympathetic autonomic nervous system improvement in sleeping hours. The results showed improved sleep quality without morning grogginess along with improved nighttime parasympathetic activity with the use of the medical food. Trazodone taken with the medical food produced greater improvement in all parameters compared to trazodone or the medical food alone [31]. Restoration of serotonin production in patients with fibromyalgia is essential to initiate restorative sleep and restore autonomic function [32]. The use of a medical food is effective for sleep disorders because serotonin production can only be normalized with nutritional management of tryptophan and 5-hydroxytryptophan as the body cannot synthesize these precursor amino acids.

Treatment of pain with a medical food has also been studied. Two double-blind placebo controlled trials were conducted to study the effectiveness of an amino acid medical food and commonly used NSAIDs in the treatment of back pain. Both trials observed the use of the medical food and the combined therapy of a medical food and an NSAID were superior to the use of an NSAID alone. Of important note, the medical food alone reduced the inflammatory markers C-

reactive protein and interleukin 6 while the NSAID group alone increased these values [33,34].

The observation that fibromyalgia is characterized by fatigue, musculoskeletal pain, sleep disturbances, poor concentration and an abnormal hormonal response to stress further suggests that imbalances in cholinergic activity is present [22,23]. Physiologic symptoms associated with Post Traumatic Stress Disorder often parallel those of fibromyalgia patients. Amino acid based medical foods may also be helpful in alleviating these related symptoms by targeting the cholinergic imbalances [35].

The Nutritional management of disease has been fundamental since the advent of therapeutic medicine. The relationship between disease, physiologic symptoms and amino acid turnover rates is becoming clear as new research and increased clinical utilization of medical foods continue to yield positive patient outcomes. The multifaceted nature of fibromyalgia suggests that a comprehensive approach to treatment which includes specific dietary interventions and use of appropriate antioxidants may be necessary to achieve optimal outcomes in patients suffering with Fibromyalgia.

## Author Disclosure Statement

The authors are employees of Targeted Medical Pharma, which is a manufacturer of medical foods, which are referenced in this article.

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