Pain Ther (2021) 10:827–848
https://doi.org/10.1007/s40122-021-00266-9

REVIEW

# The Role of Nutrient Supplementation in the Management of Chronic Pain in Fibromyalgia: A Narrative Review

Hannah Waleed Haddad · Nikita Reddy Mallepalli · John Emerson Scheinuk · Pranav Bhargava · Elyse M. Cornett · Ivan Urits · Alan David Kaye

Received: February 17, 2021 / Accepted: April 9, 2021 / Published online: April 28, 2021


## ABSTRACT

***Introduction***: The multifaceted clinical presentation of fibromyalgia (FM) supports the modern understanding of the disorder as a more global condition than one simply affecting pain sensation. The main pharmacologic therapies used clinically include anti-epileptics and antidepressants. Conservative treatment options include exercise, myofascial release, psychotherapy, and nutrient supplementation.
***Methods***: Narrative review.
***Results***: Nutrient supplementation is a broadly investigated treatment modality as numerous deficiencies have been linked to FM. Additionally, a proposed link between gut microbiome patterns and chronic pain syndromes has led to studies investigating probiotics as a possible treatment. Despite positive results, much of the current evidence regarding this topic is of poor quality, with variable study designs, limited sample sizes, and lack of control groups.
***Conclusions***: The etiology of FM is complex, and has shown to be multi-factorial with genetics and environmental exposures lending influence into its development. Preliminary results are promising, however, much of the existing evidence regarding diet supplementation is of poor quality. Further, more robust studies are needed to fully elucidate the potential of this alternative therapeutic option.

**Keywords:** CoQ10; Fibromyalgia; Hyperalgesia; Melatonin; Probiotics; Supplements; Vitamins

H. W. Haddad
Kansas City University of Medicine and Biosciences, Kansas City, MO, USA
e-mail: hhaddad@kansascity.edu

N. R. Mallepalli · J. E. Scheinuk · P. Bhargava · E. M. Cornett (✉) · I. Urits · A. D. Kaye
Department of Anesthesiology, Louisiana State University Health Shreveport, Shreveport, LA, USA
e-mail: ecorne@lsuhsc.edu

N. R. Mallepalli
e-mail: nmall2@lsuhsc.edu

J. E. Scheinuk
e-mail: jschei@lsuhsc.edu

P. Bhargava
e-mail: pbhar1@lsuhsc.edu

A. D. Kaye
e-mail: akaye@lsuhsc.edu

I. Urits
Southcoast Health, Southcoast Physicians Group Pain Medicine, Wareham, MA, USA
e-mail: ivanurits@gmail.com

**Key Summary Points**

Fibromyalgia (FM) is a clinical entity characterized by widespread physical and psychological symptoms that mainly include chronic diffuse pain and fatigue lasting ≥ 3 months in duration and sleep mood and cognitive disturbances.

The prevalence of FM worldwide is estimated to range from approximately 0.4 to 9.3%, with prevalence increasing with age.

There is a strong consensus that biological factors (inflammatory rheumatic disease, gene polymorphisms, vitamin D deficiency, thiamine deficiency), lifestyle factors (smoking, poor diet, sedentary lifestyle, and being overweight), and psychological factors (physical and/or sexual abuse in childhood, sexual violence in adulthood, and depressive disorders) have a strong association with FM.

For many patients suffering from FM, the current state of treatment for the disorder is unsatisfactory. A multimodal approach including pharmacotherapy, psychological intervention, exercise, and possibly nutrient supplementation may be more effective in managing pain symptoms.

Correlations exist between nutrition and symptoms of chronic pain. A variety of nutrient and diet alterations have shown promise in the alleviation of symptoms for those with FM. Due to a lack of sufficient high-quality evidence, more robust research is needed to clarify the efficacy of diet supplementation for FM.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14387648.

## INTRODUCTION

Fibromyalgia (FM) is a clinical entity characterized by widespread physical and psychological symptoms that mainly include chronic diffuse pain and fatigue lasting ≥ 3 months in duration and sleep mood and cognitive disturbances [1]. The etiology of FM is unclear, but it is thought to have genetic and environmental components that compound with an abnormal central nervous system (CNS) stress-response to cause dysregulation of nociception, the neural process of encoding and processing noxious stimuli, and non-nociceptive symptoms [2, 3]. FM is a clinically heterogeneous disorder due to variability in symptom severity, clustering of symptoms, and response to treatment [4].

As of a 2016 revision, the American College of Rheumatology (ACR) outlines FM diagnostic criteria as generalized pain involving at least four out of five body regions, persistent symptoms lasting at least 3 months without relief, and scores on the widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) ≥ 5 OR WPI ≥ 4–6 and SSS ≥ 9 [5]. Diagnostic criteria have evolved from a narrow emphasis on decreased pain threshold based on the number of tender points present to a more holistic review of all the patient's pain and non-pain symptoms [6].

Several studies that investigated pharmacological interventions for pain reduction in FM found only modest increases in the number of participants (10–25%) reporting ≥ 50% pain reduction compared to the placebo control group [7–10]. Alternatively, more conservative treatment approaches have shown increasing benefit. A meta-analysis evaluating the efficacy of exercise in FM found that aerobic exercise improved pain symptoms and overall well-being [11]. Further studies have confirmed that exercise may improve physical function, fatigue, and health-related quality of life of FM patients [12, 13]. Psychological intervention therapies have also shown to be effective in

improving symptoms of FM. A systemic review evaluating psychoeducation as a means to improve coping with FM reported statistically significant positive results in the majority of studies. Specific benefits such as improved functional status, pain, and mood symptoms were observed [14]. Other psychological therapies, such as practicing mindfulness, have also been associated with less pain interference and better quality of life in FM patients [15].

A systematic review by Elma et al. found evidence from seven out of nine experimental studies indicating the pain-relieving effects of a plant-based diet on chronic musculoskeletal pain. The beneficial effects are theorized to be associated with a higher intake of antioxidants and foods with anti-inflammatory and analgesic properties [16, 17]. More high-quality clinical trials and studies are needed to assess the validity of these claims. It is important for providers to emphasize all aspects of treatment and not just pharmacological options, as good sleep hygiene, a healthy diet, regular exercise, and satisfactory patient education can also alter the disorder's trajectory. The quality of the physician–patient encounter may also impact a patient's treatment adherence and reduce levels of distress and catastrophizing. Joint decision-making and reassurance of the legitimacy of complaints should be key components of the interaction [18].

Patients with FM typically present to primary care providers before eventually being referred for a rheumatologic consultation. Several barriers to diagnosing FM exist on the part of the healthcare provider (especially in primary care) due to unclear and continually changing diagnostic criteria and a lack of confidence and training on FM diagnosis/treatment [19]. On average, it takes 2 years, and 3.7 different providers before patients are diagnosed with FM and provided treatment, leading to decreased satisfaction amongst this patient population. FM is a debilitating disorder that can affect quality of life, employment, and create an economic burden on the patient [20].

# METHODS

This was a narrative review. In 2020, we performed a comprehensive search utilizing the PubMed database for studies related to "Nutrient Supplementation in the Management of Chronic Pain in Fibromyalgia." We searched the following keywords: fibromyalgia, vitamin, diet, CoQ10, hyperalgesia, melatonin, probiotics, supplements. Priority for inclusion was given to recent manuscripts (within the last 3 years), but relevant papers older than 3 years were also included. An attempt to search for, use, and cite primary manuscripts whenever possible was also made. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## Fibromyalgia Epidemiology/ Pathophysiology/Risk Factors/ Presentation

### *Epidemiology*

The prevalence of FM worldwide is estimated to range from approximately 0.4 to 9.3%, with prevalence increasing with age [1]. It is the second most common disorder seen by rheumatologists, after osteoarthritis, and is thought to affect 5 million individuals in the United States [21]. Several studies corroborate a higher prevalence of FM in women than men, with the ratio ranging up to 4:1, especially during childbearing years [22–25]. FM has also shown to be much more prevalent amongst overweight (30%) and obese (40%) populations [26]. FM is commonly reported with other chronic pain conditions such as irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), vulvodynia, temporomandibular disorders, chronic tension-type headaches, and chronic migraine headaches [3, 7, 27, 28]. A recent meta-analysis showed a higher prevalence of FM in those undergoing hemodialysis and with comorbidities such as type II diabetes mellitus and Behçet's disease [29].

### *Pathophysiology*

People with FM often have allodynia, an abnormal hypersensitivity to non-nociceptive stimuli, and hyperalgesia, a pain response out of proportion to the typical response from that stimuli. These two characteristics are hallmarks of "central sensitization," or hyperexcitability of central neurons due to blunting of inhibitory pain pathways and alterations in neurotransmitter levels [30]. This widespread pain phenomena in patients suggests abnormalities in central pain processing rather than localized disease.

Increased central sensitization occurs due to abnormalities in ascending and descending pain pathways. Glutamate, substance P, and nerve growth factor (NGF) have all been found in increased concentrations in the spinal fluid of FM patients, demonstrating evidence for increased neuronal excitability and therefore decreased pain threshold [31–34].

While the exact pathophysiology of FM is still unclear, several studies have implicated disruptions in various inflammatory pathways [35]. Pro-inflammatory cytokines, IL-IRA, IL-6, and tumor necrosis factor-alpha (TNF-α), and chemokine, IL-8, are increased in FM, and anti-inflammatory cytokine (IL-4) is decreased. This is thought to contribute to chronic neuroinflammation and sensitization of central and peripheral nociceptors [30, 36–38]. Pro-inflammatory cytokines increase prostaglandin levels and upregulate substance P release, leading to a decreased pain threshold [30].

Dysfunctions of the bodies' central stress mechanisms have been hypothesized to modulate pain sensitivity in FM. Studies have documented the existence of basal hypocortisolism in FM suggesting an abnormality of the hypothalamic–pituitary–adrenal (HPA) axis in response to stress. Hypocortisolism has been linked to a history of chronic stress or trauma and may be a consequence of increased sensitivity to glucocorticoid receptors responsible for HPA axis negative feedback. The HPA axis helps modulate the sympathetic nervous system (SNS) via glucocorticoids inhibiting norepinephrine (NE). Hypocortisolism may play a role in the hyperactivity of the SNS causing increasing levels of NE which may repress the opioid–peptide system responsible for stress-induced analgesia. This may contribute to the decreased pain threshold observed in FM patients. Hypocortisolism has been reported in other stress-related disorders such as post-traumatic stress disorder or CFS [39–41].

The presence of oxidative stress leading to increased neuroinflammation has also been implicated in FM, but the exact mechanism by which it may cause symptoms has not yet been elucidated [42, 43]. Decreased blood lysate levels of catalase, glutathione peroxidase, and glutathione reductase previously seen in FM may lead to decreased clearance of free radicals and increased plasma levels of lipid peroxides and protein carbonyls resulting in higher levels of oxidative stress. The severity of these abnormalities is thought to reflect the severity of FM symptoms [44]. Additional studies implicating oxidative stress in FM pathogenesis found evidence of mitochondrial dysfunction, increased mitochondrial reactive oxygen species (ROS), and reduced coenzyme Q10 ($CoQ_{10}$) [45, 46].

### *Risk Factors*

While the etiology of FM remains unclear, there is a strong consensus that biological factors (inflammatory rheumatic disease, gene polymorphisms, vitamin D deficiency, thiamine deficiency), lifestyle factors (smoking, poor diet, sedentary lifestyle, and being overweight), and psychological factors (physical and/or sexual abuse in childhood, sexual violence in adulthood, and depressive disorders) have a strong association with FM [16, 47–50]. Risk factors may be categorized as distal (childhood trauma, smoking, low IQ), intermediate (medical comorbidities), and proximal (current somatic symptoms). Many somatic symptoms, such as fatigue, headaches, depression, and cognitive symptoms, are now recognized by the ACR diagnostic criteria as being a component of FM [24]. Additionally, epidemiological and experimental studies have found that poor sleep quality is not only a symptom of FM but also a risk factor for its development [51, 52].

Genome-wide linkage analyses show several gene polymorphisms that occur at higher frequencies in FM populations, including those responsible for the 5-HT2A serotonin receptor

protein, 5-HTT serotonin transporter protein, catecholamine-*o*-methyl transferase (COMT) enzyme, DRD3 dopamine receptor protein, and various adrenergic receptor proteins. These genetic alterations could potentially be responsible for decreased pain threshold and/or various psychological and somatic symptoms present in FM; the exact mechanism by which these genetic alterations may play a role in FM has not yet been discovered, and contradictory findings indicate the need for further investigation [53–59].

### *Presentation*

The classic presentation of FM includes widespread chronic pain, fatigue, and sleep disturbance that persists for at least 3 months. This triad of symptoms is most commonly seen in FM patients and are considered core diagnostic criteria according to the Addiction Clinical Trial Translation, Innovations, Opportunities, and Networks-American Pain Society-and American Academy of Pain Medicine (ACTTION-APS-AAPM) Acute Pain Taxonomy (AAPT) and FM Working Group and Outcome Measures in Rheumatology (OMERACT) [20]. Many other symptoms, such as tenderness, cognitive dysfunction, musculoskeletal stiffness, sexual dysfunction, and environmental hypersensitivity (noise, weather, temperature), are commonly seen in FM but are not required for diagnosis [60, 61]. Other pain symptoms such as abdominal and chest wall pain are rarely present and not well understood in FM [5]. Additionally, psychological comorbidities are commonly presented with FM. The most common psychiatric conditions include depressive disorders, anxiety disorders, and substance abuse disorder [20, 25, 62]. A diagnosis of FM is made based on patient history and physical exam findings; however, laboratory screening for other medical conditions and rheumatic diseases can be obtained to rule out other causes of a patient's symptoms. Oftentimes, patients will have complaints of swollen joints and paresthesia without any objective findings upon physical exam [3].

## Current Treatment of Fibromyalgia

For many patients suffering from FM, the current state of treatment for the disorder is unsatisfactory. Despite the European League Against Rheumatism's (EULAR) push to move from recommendations based on expert opinions to that based on evidence-based research, treatment effect has been overall very modest [63].

There are two main classes of pharmacotherapeutics prescribed for FM: anti-epileptic drugs (AEDs) and anti-depressants. The antidepressants utilized are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitor (SSRIs), and serotonin-norepinephrine reuptake inhibitor (SNRIs). However, pregabalin, duloxetine, and milnacipran are the only FDA-approved drug treatments for FM, and all other treatment is considered off-label [64, 65]. Pregabalin was the first drug approved by the FDA for FM treatment but has only shown modest reductions in pain and sleep problems upon thorough review. The results of several placebo-controlled studies indicate that duloxetine may improve pain and depressive symptoms, but not fatigue or sleep disturbance. Alternatively, milnacipran has been shown in multiple placebo-controlled studies to improve pain and fatigue, but not depressive symptoms or sleep disturbances [64, 66]. About 40% of patients report having moderate (30%) relief from milnacipran [67]. While not FDA-approved, TCA amitriptyline was found to be superior to both SNRIs, duloxetine, and milnacipran in reducing pain, sleep disturbances, and fatigue in a meta-analysis of ten placebo-controlled amitriptyline studies. However, methodological limitations, such as the length of the trial, prompt a more robust study of the use of amitriptyline in FM treatment [64, 68]. While SSRIs are recommended for FM treatment as per EULAR and Canadian guidelines, their usage is largely only useful for the treatment of depressive symptoms in FM patients [69]. Analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, are frequently used by FM patients, despite the lack of proven efficacy in FM treatment [63].

Combination therapy for synergistic action of the main pharmacotherapeutics is a new avenue for consideration; however, clinical trials are needed to establish safety and potential increases in efficacy [70]. Many pharmacologic therapy options for FM patients are not well tolerated due to increased sensitivity to side effects and have varied efficacy due to the heterogeneous patient population [65]. It is important to start conservatively with low-dose pharmacological treatment and encourage physiotherapy, coping strategies, and psychoeducation. Non-pharmacological therapies such as exercise, hydrotherapy, myofascial release massage therapy, and meditative movement therapy have also shown modest improvements in FM symptoms. A multi-modal approach to treatment incorporating aspects of pharmacology, psychological intervention, and exercise have been associated with improved clinical outcomes [18, 63, 64].

Non-invasive neurostimulation therapies such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have been studied as therapeutic options to reduce pain perception in FM. Both tDCS and rTMS have shown to effectively reduce pain and depressive symptoms by stimulating the primary motor cortex and the dorsolateral prefrontal cortex [71, 72]. It is hypothesized that neurostimulation therapies modify pain processing in thalamocortical systems [73]. These therapies are reportedly associated with minimal risk and may offer significant improvement in FM symptoms [74].

Hyperbaric oxygen therapy (HBOT) may be used to regulate the increased oxidative stress implicated in the pathogenesis of FM. Mitochondrial dysfunction, as seen in FM, leads to local hypoxia and muscular degeneration resulting in muscle weakness and pain. Hyperoxia from HBOT may improve FM symptoms by preventing oxidative damage during reperfusion, restoring mitochondrial function, reducing apoptosis, and producing an anti-inflammatory response [75, 76]. Clinical trials testing HBOT for the treatment of chronic pain conditions, including complex regional pain syndrome, myofascial pain syndrome, idiopathic trigeminal neuralgia, and cluster headaches, have successfully shown increases in pain threshold [77–80].

The implementation of plant-based diets and nutrient supplementation has been investigated in FM with contradicting results. It is important to note that much of the current evidence regarding this topic is of poor quality, with variable study designs, limited sample sizes, and lack of control groups. Keeping this in mind, there is some evidence that nutrient supplementation may have a role in the treatment of FM. Recent studies indicate FM patients may have a lower qualitative and quantitative diet when compared to healthy individuals. Reduced caloric intake and consumption of carbohydrates, proteins, lipids, vitamins A, E, K, folate, selenium, and zinc have been reported. Additionally, a positive correlation between protein intake and pain threshold, and an association between vitamin E and quality of life, has been documented [16, 81, 82].

As previously stated, a multi-disciplinary approach to symptom management is associated with improved clinical outcomes in FM [18, 63]. Nutritional supplementation may be an additive approach in this model. More robust research is needed to further clarify the benefit of this treatment modality. Further elaboration into the investigation of nutrient supplementation follows below.

## The Role of Nutrient Supplementation for Pain Management in Patients with Fibromyalgia

Chronic musculoskeletal pain may go beyond the traditional psychological and cognitive approach to which it is often attributed. In fact, the WHO points out the role that diet can have in modulating pain in the body and recognizes its importance as a “modifiable determinant” of pain. For example, eicosapentaenoic acids, arachidonic acids, and tryptophan, all of which are essential fatty acids, have been linked in producing pain-relieving effects at the CNS level [16]. However, the idea that vitamins and nutritional supplements directly correlate to the pathophysiology of the disease is one that is disputed. In fact, some research has found no

statistical correlation between the use of supplementation and the effectiveness for patients [81]. One study looked to examine the correlation between monosodium glutamate (MSG) intake and the symptoms of FM; patients that discontinued the consumption of MSG tended to have similar levels of pain as those in the control group. To add, the authors of the study cautioned against unreliable accounts of nutritional supplementation being used for chronic pain and warned that it could create false confidence for many patients [83].

### *Nutritional Links*

While there is conflict among the scientific community on this topic, many have found correlations that exist between nutrition and symptoms of chronic pain. A variety of nutrients, diets, and vitamins have shown promise in the alleviation of symptoms for those with FM. One study concluded that, in some patients, dietary glutamate might have an influence on FM symptoms. Out of 37 individuals that completed a glutamate and aspartame-free diet, 84% reported that > 30% of their initial symptoms resolved [84]. Another diet that is low in "fermentable oligo-, di-, or monosaccharides and polyols" (FODMAP) has been looked at with promising results in symptomatic relief of IBS and FM. A longitudinal study with FM patients showed a marked reduction in both FM symptoms and pain scores after the low FODMAP diet was implemented [85, 86]. Additionally, a survey conducted among FM patients showed that 30% of patients tried dietary supplements or made some type of dietary change in response to their disease, with 74% of these patients making these changes in accordance with their healthcare professionals. These individuals reported pain relief, noting that the addition of magnesium was especially effective [87].

Antioxidants are yet another nutritional supplement that shows promise in the management of FM. As previously mentioned, oxidative stress may be a culprit in the pathogenesis of FM. Superoxide dismutase (SOD), an enzyme that breaks down ROS, plays an important role in mitigating free radical damage in the body. Significantly elevated SOD activity was observed in female patients with FM as compared to a control group of healthy individuals without FM [88]. Vitamin C and E (VCE) supplementation has shown some success in reducing FM-induced oxidative stress through upregulating enzymatic antioxidants in plasma and erythrocytes. A study of 32 women with FM who supplemented with VCE for 12 weeks had increased protective glutathione peroxidase activity, an antioxidant enzyme, in erythrocytes when compared to baseline. Furthermore, the protective effect of VCE supplementation was greater when combined with exercise. It is important to note, however, that no significant improvement in FM symptoms was observed [89]. Despite lack of symptom relief, this study may indicate that VCE plus exercise may be able to help lower ROS levels, which may be promising for those with FM.

FM proves to have complex, multifactorial pathophysiology that may require both pharmacological and nonpharmacological approaches. While the effects of nutrition and diet alteration may be disputed, research has shown some benefit. Additional high-quality research is required before practitioners can be certain of which supplemental approaches to advise [90].

## Vitamins B9 and B12 in the Management of Fibromyalgia

Vitamin B9 (folic acid) and B12 (cobalamin) may be potential constituents in the management of FM. One clinical study examined FM patients' self-reported response after frequent B12 injections with additional B9 oral supplementation. It was reported that the B12 injections with oral B9 were useful for symptom relief in FM patients. However, this supplementation treatment did present with confounding variables. The treatment seemed to be less effective in patients using opioids to manage pain; this is thought to be due to the increased methylation of the analgesic that may prevent it from having its strongest pain-relieving effect. In addition, patients taking thyroid hormones due to hypothyroidism proved to have the greatest relief from the B12 and B9 treatment; this may be due to a relationship

that exists between FM and thyroid imbalance [91]. Both vitamins B12 and B9 are cofactors in the metabolism of homocysteine (HCY). Studies have shown that increased plasma HCY can be linked to neurological and psychiatric disorders. An analysis of serum plasma and cerebrospinal fluid (CSF) from healthy individuals revealed an association between serum and CSF concentrations of HCY, vitamin B9, and vitamin B12. Increases in serum-HCY were associated with increases in CSF-HCY, higher CSF-HCY was associated with lower CSF-B9 when serum B9 levels were $< 25$ nmol/l, serum-HCY $> 10.8$ μmol/l was associated with reduced CSF-B9, and lower levels of serum-B12 may indirectly increase the amount of CSF-HCY. This highlights that low serum B9 and B12, or B9/B12 deficiency, may lead to increased HCY in the CSF, which is considered a risk factor for neurological disease. The analysis concluded that increased amounts of vitamins B12 and B9 may lower the CSF-HCY concentration [92]. Lowering HCY levels in the CSF could have a positive effect on the outcomes of neurological disorders. One clinical study highlighted the relationship between HCY levels and patients suffering from FM. They found that patients with FM had a positive correlation between their CSF-HCY concentration and level of fatigue. Vitamin B12 deficiency may be a cause of increased CSF-HCY due to HCY not efficiently being remethylated [93]. Though this research is promising, other studies have failed to prove a connection between B12 deficiency and FM [94]. More research is needed to sort out the implication of these findings for FM patients as they may indicate a future for the management of the disease.

Vitamin B12 may also have a significant role as an acute analgesic, which can be used to alleviate chronic pain. Numerous studies and publications have highlighted the positive analgesic effects of vitamin B12 [95–97]. One clinical study examining the analgesic effects of vitamin B12 found that individuals receiving an intramuscular injection of methylcobalamin three times a week for 2 weeks showed a statistically significant decrease in reported pain scores as compared to a control group receiving normal saline for an equivalent time. There are a few reported theories highlighting the mechanism of B12's analgesic effect. One such theory is based on B12's inhibition of inflammatory mediators, and another is based on B12's ability to enhance the efficiency of noradrenaline and 5-hydroxytriptamine as inhibitory signals in the pain pathway [95]. Another proposed mechanism of its analgesic effect is through the promotion of injured nerve regeneration and inhibition of spontaneous ectopic neuron activity. It is reported that ectopic spontaneous firing of neurons is linked to unprompted pain and enhanced sensitivity to pain. Vitamin B12 has also been shown to play a role in modulating nerve conduction velocity, as reported by previous studies showing high doses of methylcobalamin improving nerve conduction velocity in patients with diabetic neuropathy [96]. Through various mechanisms, both vitamin B12 and B9 may have use in the management of chronic pain symptoms in FM patients.

## Magnesium, Calcium, and Tryptophan in the Management of Fibromyalgia

Another studied approach in the management of FM includes the use of magnesium and calcium. The conclusions on the efficacy of these minerals varies. One meta-analysis reported that magnesium supplementation has an undetectable influence on pain and depressive symptoms in FM patients [98]. Contrarily, a clinical trial investigating the effect of transdermal magnesium therapy on women with FM reported significant improvement of self-reported FM symptoms. This study underlines the potential of transdermal magnesium, though the study lacked a control group for comparison [99]. Furthermore, dietary intake of magnesium and calcium are lower in patients diagnosed with FM. Interestingly, dietary intake of magnesium and calcium can have a direct correlation to pain threshold and an inverse relationship to tender point count in patients with FM [100]. This highlights the potential association between magnesium and calcium levels and the severity of disease in FM.

One proposed theory of the analgesic effects of magnesium implicates magnesium's

antagonism of the *N*-methyl-D-aspartate (NMDA) receptor. NMDA receptors are located in the CNS and allow for the inflow of sodium and calcium and outflow of potassium. Inhibition of the NMDA receptor reduces central sensitization and diminishes established pain hypersensitivity. Central sensitization is directly related to the increased intracellular calcium that is a result of the excitation of the NMDA receptor. Magnesium therapy can reduce the pain intensity of patients with low back pain and improve lumbar spine range of motion in the same patient population. While magnesium works to block NMDA receptors, glutamate, substance P, and calcitonin gene-related peptide (CGRP) cause depolarization leading to NMDA channel opening. Magnesium deficiency may lead to increases in substance P concentration. Additionally, substance P is linked to the pain intensity of FM. Therefore, it is possible that magnesium can be advantageous for the management of symptoms in FM patients [101].

A randomized control trial of only 22 women with FM found a tryptophan- and magnesium-rich diet can improve anxiety, fatigue, psychological disturbances, self-image perception, and eating disorders symptoms. Low serotonin levels have been linked to FM, therefore, adequate intake of tryptophan, a serotonin precursor, may help alleviate FM symptoms [102]. Furthermore, animal studies suggest that tryptophan supplementation may reduce cortisol concentration and pain sensitivity in rats [103]. Despite promising preliminary results, additional investigation is needed before recommending magnesium, calcium, or tryptophan for symptom relief in FM.

## Vitamin D in the Treatment of Fibromyalgia

The role of vitamin D deficiency in chronic pain syndromes has become an increasingly popular topic in light of research that has shown various ways that vitamin D modulates pain. Vitamin D has been shown to influence nociceptive innervation on skeletal muscle, resulting in hyperinnervation and hypersensitivity to musculoskeletal pain when deficient [104]. In 2018, Wu et al. [105] published an observational study of 50,834 participants where significantly lower 25(OH)D levels were observed in patients with chronic widespread pain. Furthermore, a 2017 meta-analysis concluded that vitamin D supplementation can reduce pain scores and improve pain symptoms in chronic widespread pain syndromes including FM [106].

The connection between vitamin D and FM has been widely studied [107–121]. However, the relationship between vitamin D deficiency and FM is controversial among literature. A 2017 meta-analysis of 12 studies, found in eight studies the mean level of vitamin D was lower in FM cases when compared to controls. This study concluded that serum vitamin D levels are significantly reduced in patients with FM [107]. A 2018 systemic review additionally concluded an association between vitamin D deficiency and FM [108]. Contrarily, a 2020 systematic review of 16 studies examining hypovitaminosis D in FM patients reported only six studies showing vitamin D deficiency in FM patients. This study concluded that vitamin D deficiency is likely unrelated to the pathophysiology of FM and the differences among studies is attributed to the deficiency being commonly found in the general population [109]. Lastly, a recent cross-sectional study also found no significant difference in vitamin D levels between those with and without FM. They did, however, conclude that low vitamin D levels may predict more severe disease symptoms [110].

Several mechanisms of the role of vitamin D in the pathophysiology of FM have been proposed. Vitamin D is involved in brain development, neuronal regulation, increases in neuronal growth factors, and neuroprotective effects. Vitamin D can reduce neuronal excitability thresholds affecting action potential duration and sensitivity to neurotransmitters and neurotransmitter receptors. Additionally, vitamin D may have a positive effect on the production of glial cell line-derived neural growth factor (GDNF), which functions as a protective neuropeptide that may promote the maintenance of sensory and sympathetic neurons. Studies show reduced CSF concentrations of GDNF in FM patients, further implicating its potential importance in the disease process.

Furthermore, vitamin D has been linked to the upregulation of transforming growth factor beta 1 (TGF-B1). TGF-B1 directly opposes inflammatory cytokines that are regularly seen elevated in FM patients. Vitamin D is also known to be a part of regulating bone mineral density (BMD). There is some evidence that reduced BMD is linked to the severity of FM pain, however, this correlation lacks substantial evidence [111].

Recent studies have explored the role vitamin D may play on specific symptoms of FM. D'Souza et al. reported FM patients with hypovitaminosis D had increased symptom severity, anxiety, and depression when compared to FM patients without vitamin D deficiency [112]. Vitamin D deficiency was also shown to negatively affect balance in FM patients [113]. Reduced serotonin levels have shown to be linked to vitamin D deficiency and symptom severity in FM. Brain serotonin is synthesized from tryptophan via an enzyme activated by vitamin D, and a dose-dependent negative relationship between serotonin levels and FM impact questionnaire scores has been reported [114, 115].

Other clinical studies have investigated the possible importance of vitamin D in FM. A randomized placebo-controlled trial concluded that adequate vitamin D levels had a positive effect on the perception of pain in FM [116]. Another randomized control trial concluded that vitamin D supplementation was beneficial in reducing pain in FM. A combination of vitamin D supplementation and an anti-depressant showed further improvement in physical and psychological symptoms [117]. Additional studies have also found vitamin D supplementation may provide significant relief of FM pain symptoms in patients with preexisting vitamin D deficiency [118–120]. Further support of these findings was provided by Abou-Raya et al. [121] who found a significant reduction in pain and significant improvement in physical function in FM patients receiving vitamin D supplementation as compared to a placebo. Vitamin D may be a cheap and beneficial adjunctive treatment in the management of FM.

## Melatonin in the Treatment of Fibromyalgia

An essential hormone of the pineal gland, melatonin is widely known for its role in circadian physiology. It is also implicated in analgesic, antioxidant, and anti-inflammatory roles [122]. Additionally, while it is classically produced in the pineal gland, many organ systems have been discovered as sources of melatonin over the years, including skeletal muscle, gastrointestinal tract, immunologic cells, liver, spleen, and others [123, 124]. Melatonin is implicated in many regulatory roles, such as protective effects against obesity, diabetes, depression, and anxiety, but it has also been implicated in anti-nociceptive roles, giving it cause for investigation as a therapeutic in FM [125–127].

Melatonin (*N*-acetyl-5-methoxy tryptamine) was considered to be exclusively produced by the pineal gland until it was identified in numerous other exogenous sources. Plants, insects, fungi, and bacteria have all been found to contain melatonin [128–131]. Given these discoveries, edible plants and animal meats have been evaluated for melatonin content. These studies revealed a broad range of melatonin content in various dietary sources, with some sources providing significant amounts [132, 133]. Given this evidence that melatonin has more roles than just circadian physiology and more sources than just the pineal gland, the role of melatonin in pain regulation as a possible therapy for FM has received greater attention. Several mechanisms have been suggested for melatonin's role in the regulation of pain, but none have been definitively identified as the known mechanism. Those suggested include $G_i$-coupled melatonin receptors, $G_i$-coupled opioid μ-receptors, or gamma-aminobutyric-B (GABA-B) receptors regulating anxiety and pain [134–141]. One potential mechanism that is better understood is melatonin's role in sleep regulation and its consequential reduction in anxiety, which may therefore reduce pain perception [142].

Several studies have identified altered levels of plasma and urine melatonin in FM patients as compared to controls. However, these studies

found differing results, including elevated, decreased, and equivocal levels of melatonin in FM patients [143–145]. With the discovery of mitochondria being strong melatonin producers, and skeletal muscle's high concentration of mitochondria, a link between FM and melatonin appears possible [146–148].

Already, several experimental studies have been conducted evaluating melatonin's role in pain relief. Specifically, FM has been a focal point as a chronic pain condition that may benefit from medication with few side effects such as melatonin. In a review of multiple experimental studies, melatonin supplementation led to an improvement in several outcome measures of FM, including disease impact, sleep quality, pain level, and tender point count. Contrarily, the studies did not find conclusive evidence that melatonin improves anxiety, fatigue, or depression in FM patients [142, 149–151].

Though the evidence thus far suggests that melatonin may have a role in pain relief in FM, a definitive answer is more likely with better-controlled experimental studies in the future. The studies referenced here identified possible areas of confounding that may affect results, many of which may be corrected by altered study designs.

## Coenzyme Q10 in the Treatment of Fibromyalgia

$CoQ_{10}$ is the electron carrier between complexes I and II of the electron transport chain in mitochondrial ATP production, making it a critical aspect of the body's ATP production capacity [152]. Additionally, $CoQ_{10}$ has been suggested to have antioxidant properties [153]. Various stressors may affect $CoQ_{10}$ levels in the body, but it is known that myopathies feature reduced $CoQ_{10}$ levels, whether as a cause or effect of the myopathy remains to be determined [154]. Because FM is a chronic pain syndrome with myopathic features, $CoQ_{10}$ levels have been evaluated in patients with FM to assess for altered levels and distributions compared to those without FM. It should be noted that despite having proven $CoQ_{10}$ deficiency, plasma levels of $CoQ_{10}$ may remain unchanged and in normal range, making plasma $CoQ_{10}$ levels a poor marker of overall tissue levels and body stores [155]. There appears to be a positive correlation between skeletal muscle $CoQ_{10}$ stores and mononuclear cell $CoQ_{10}$ content, potentially making mononuclear cell analysis a better diagnostic marker [156]. With this in mind, several reviews have concluded that patients with FM often have coexisting $CoQ_{10}$ deficiencies [153, 157, 158].

In patients with $CoQ_{10}$ deficiencies, repletion with $CoQ_{10}$ is a proposed treatment method to alleviate symptomatic coexisting conditions, including FM. The mechanisms of FM symptomatic improvement after $CoQ_{10}$ supplementation are not entirely understood, but several mechanisms are proposed. One relates to the role of $CoQ_{10}$ in the mitochondrial electron transport chain and the high concentration of mitochondria in skeletal muscle [155]. In FM patients with myopathic symptoms, mitochondrial dysfunction secondary to $CoQ_{10}$ deficiency may have a significant role in symptom severity, and patients have shown improvement following $CoQ_{10}$ supplementation [153, 158–161]. This symptomatic benefit cannot reasonably be entirely attributed to improving mitochondrial function. $CoQ_{10}$ has potent antioxidant and free radical scavenger properties, which may also effect the pathogenesis of FM due to the role of ROS in causing hyperalgesia. Supplementation with $CoQ_{10}$ has demonstrated the ability to correct the increased ROS production and improve FM symptoms [45, 160–163].

More recently, the AMP-activated protein kinase (AMPK) cascade has been implicated in the overall effect that $CoQ_{10}$ has in FM [157, 160]. AMPK is referred to as the overall regulator of cellular energy levels [164]. The effects of $CoQ_{10}$ mentioned above may be under the control of AMPK gene expression and its downstream effects on energy regulation as a possible mechanism for symptomatic improvement in FM [160]. The data thus far are sparse on this topic, but it is an emerging theory that warrants further investigation.

## Probiotics in the Management of Fibromyalgia

The gut microbiome is increasingly a subject of research in non-gastrointestinal disorders as links between gut homeostasis and the pathophysiology of various conditions, particularly CNS disorders, are elucidated [165–168]. Although the most prominent symptoms of FM are pain-related, gastrointestinal symptoms appear in a large portion of patients with FM [28]. In fact, nearly 81% of FM patients in one study reported fluctuating between normal and irregular bowel patterns, while a smaller portion reported fluctuating specifically between diarrhea and constipation [169]. Several other studies focused specifically on whether patients with FM meet the diagnostic criteria for IBS and found that between 32 and 80% of patients with FM meet these criteria, further strengthening a gastrointestinal association [170–173]. Additionally, numerous studies have found associations between the gut microbiome, including specific bacterial colonization patterns, and FM and CFS, a closely associated condition to FM [174–176]. In particular, one study that focused on gut microbiome patterns suggests the association between gut microbiome and chronic pain syndromes (including FM) may be strong enough that microbiome analysis may be useful as a diagnostic test [177].

The literature is lacking in thorough, large, and well-controlled experimental studies on probiotics in the treatment of FM. However, a review article on CFS indicates a potential benefit. In patients with CFS, the preeminent outcome measures which treatments focus on relate to psychiatric and inflammatory processes. These studies found that probiotic supplementation versus placebo led to significant changes in specific fecal bacteria and improvements in patients' anxiety. Depression was also measured but was not significantly improved in the probiotic group. Inflammatory processes, measured by serum C-reactive protein, TNF-α, and interleukin-6 (IL-6), were significantly decreased in the probiotic group of patients with CFS, compared to their baseline [178, 179]. Since CFS is closely associated with FM, these results advocate for future research on probiotics in the treatment of FM. Of the available evidence, numerous studies of conditions closely related to FM, such as IBS and CFS, demonstrated inconsistent results between studies [180]. While this indicates a placebo effect, it reiterates the complex pathophysiology of FM and supports future research on the gut microbiome and CNS association.

While the literature has an interest in various novel treatments for FM, there is insufficient evidence at present to support probiotics as a treatment for FM. However, initial studies appear to demonstrate an association and warrant further investigation.

## Iron in the Management of Fibromyalgia

Several studies have investigated serum iron levels and FM, with many agreeing that an association is present between the two. One study found that iron deficiency anemia was significantly more common in patients with FM than in a control group [181]. Another study found lower ferritin levels in patients with FM, suggesting decreased iron stores in these patients versus patients without FM [182]. Iron deficiency is highly associated with and may be a marker of chronic inflammation. Comorbid chronic inflammatory illness may be linked to FM symptoms. Furthermore, animal models suggest a relationship between iron deficiency and alterations in pain sensation, with elevated cell activity levels in the spinal cord as measured by c-Fos expression in immunoreactive cells [183]. These animal studies are pertinent to FM patients as altered pain sensation is one of the pathophysiologic hallmarks of FM. Not all literature is in agreement, however, regarding the relationship between iron and FM, and one case–control study did not find any significant relationship between FM and iron levels [184]. It should also be noted that the effect, if any, of iron deficiency on FM may or may not feature concomitant iron-deficiency anemia [182].

The proposed mechanism of the association between iron deficiency and mood and behavioral changes is iron's role as a cofactor for several enzymatic synthesis reactions. Iron is essential for serotonin synthesis via tryptophan

hydroxylase and for norepinephrine and dopamine synthesis via tyrosine hydroxylase [182]. FM, whose mechanism is likely multifactorial in nature, causes patients to experience pain differently than in those without FM. Previous studies have found decreased concentrations of biogenic amine metabolites, which include dopamine, norepinephrine, and serotonin, in the CSF of patients with FM [185, 186]. These results suggest that iron deficiency may lead to a deficiency of several enzymatically derived hormones that regulate mood with a possible subsequent effect on pain perception.

With a proposed link between FM and iron deficiency, evidence suggests that iron supplementation in iron-deficient patients with FM improves outcome measures in FM symptom severity. A blinded, randomized, placebo-controlled trial found that supplementation with ferric carboxylase improved symptoms of FM as measured by several symptom scoring systems. However, significance was not achieved in the study's primary outcome measure compared to the placebo group [187]. This result underscores the need for further studies of iron's role in FM pathophysiology, and FM's pathophysiology as a whole.

## CONCLUSIONS

Fibromyalgia is a far-reaching and systemic disorder. The understanding of FM has evolved; the recently updated holistic diagnostic criteria suggest there are more subtle symptoms of the disorder than previously thought. The non-pain symptoms of FM support the modern understanding of the disorder as a more global condition than one simply affecting pain sensation. The evolution of the proposed pathophysiology of FM includes inflammation, oxidative stress, and neurotransmitter disruptions. Many risk factors have been proposed but genetics and environmental exposures can both affect the development of FM. Currently, the main pharmacologic therapies for FM include anti-epileptics and anti-depressants. Only three specific drugs are approved by the FDA to treat FM. Numerous treatment modalities have been or are currently under investigation. There is evidence that exercise and psychological therapies are beneficial in therapeutic management. Nutrient supplementation is a broadly investigated treatment modality as numerous nutrient and vitamin deficiencies have been linked to FM. Additionally, hormone and coenzyme supplementation have been investigated with melatonin and $CoQ_{10}$. A proposed link between gut microbiome diversity in patients with FM suggests probiotics as a possible treatment modality. Preliminary results are promising, however, much of the existing evidence regarding diet supplementation is of poor quality. Further, more robust studies are needed to fully elucidate the potential of this alternative therapeutic option.

## ACKNOWLEDGEMENTS

***Funding.*** No funding or sponsorship was received for this study or publication of this article.

***Authorship.*** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

***Authors' Contributions.*** Hannah W. Haddad – concept and design, literature review, drafting and editing the manuscript; Nikita R. Mallepalli – drafting the manuscript; John E. Scheinuk – drafting the manuscript; Pranav Bhargava – drafting the manuscript; Elyse M. Cornett- editing the manuscript; Ivan Urits – concept and design; Alan D. Kaye – editing the manuscript.

***Disclosures.*** The authors Hannah W. Haddad, Nikita R. Mallepalli, John E. Scheinuk, Pranav Bhargava, Elyse M. Cornett, Ivan Urits, and Alan D. Kaye have nothing to disclose.

***Data Availability.*** Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

***Compliance with Ethical Guidelines.*** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.



## REFERENCES

1. Arnold LM, Clauw DJ. Challenges of implementing fibromyalgia treatment guidelines in current clinical practice. Postgrad Med. 2017;129(7):709–14.

2. Arnold LM, Hudson JI, Hess EV, Ware AE, Fritz DA, Auchenbach MB, et al. Family study of fibromyalgia. Arthritis Rheum. 2004;50(3):944–52.

3. Kaltsas G, Tsiveriotis K. Fibromyalgia. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000. https://www.ncbi.nlm.nih.gov/books/NBK279092/.

4. Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, et al. Subgrouping of fibromyalgia patients on the basis of pressure–pain thresholds and psychological factors. Arthritis Rheum. 2003;48(10):2916–22.

5. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016;46(3):319–29.

6. Häuser W, Wolfe F. Diagnosis and diagnostic tests for fibromyalgia (syndrome). Reumatismo. 2012;64(4):194–205.

7. Häuser W, Perrot S, Clauw DJ, Fitzcharles MA. Unravelling fibromyalgia—steps toward individualized management. J Pain. 2018;19(2):125–34.

8. Häuser W, Urrútia G, Tort S, Üçeyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Cochrane Database Syst Rev. 2013;2013:1.

9. Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. Cochrane Database Syst Rev. 2016;2016:9.

10 Üçeyler N, Sommer C, Walitt B, Häuser W. Anticonvulsants for fibromyalgia. Häuser W, editor. Cochrane Database Syst Rev. 2013;2013:10.

11. Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev. 2013;2013(12):CD010884.

12. Bidonde J, Busch AJ, Schachter CL, et al. Aerobic exercise training for adults with fibromyalgia. Cochrane Database Syst Rev. 2017;6(6):CD012700.

13 Bidonde J, Busch AJ, Schachter CL, et al. Mixed exercise training for adults with fibromyalgia. Cochrane Database Syst Rev. 2019;5(5):CD013340.

14. Conversano C, Poli A, Ciacchini R, Hitchcott P, Bazzichi L, Gemignani A. A psychoeducational intervention is a treatment for fibromyalgia syndrome. Clin Exp Rheumatol. 2019;37(1):98–104.

15. Pleman B, Park M, Han X, et al. Mindfulness is associated with psychological health and moderates the impact of fibromyalgia. Clin Rheumatol. 2019;38(6):1737–45.

16. Elma Ö, Yilmaz ST, Deliens T, Coppieters I, Clarys P, Nijs J, et al. Do nutritional factors interact with chronic musculoskeletal pain? A systematic review. J Clin Med. 2020;9(3):702.

17 Boros S. The role of nutrition in the treatment of chronic musculoskeletal diseases. J Exerc Sports Orthopedics Symbiosis Group. 2017;2017:4.

18. Petzke F, Brückle W, Eidmann U, Heldmann P, Köllner V, Kühn T, et al. General treatment principles, coordination of care and patient education in fibromyalgia syndrome: updated guidelines 2017 and overview of systematic review articles. Schmerz. 2017;31(3):246–54.

19. Hadker N, Garg S, Chandran AB, Crean SM, McNett M, Silverman SL. Primary care physicians' perceptions of the challenges and barriers in the timely

diagnosis, treatment and management of fibromyalgia. Pain Res Manag. 2011;16(6):440–4.

20 Arnold LM, Bennett RM, Crofford LJ, Dean LE, Clauw DJ, Goldenberg DL, et al. AAPT diagnostic criteria for fibromyalgia. J Pain. 2019;20:611–28.

21 Clauw DJ, Arnold LM, McCarberg BH. FibroCollaborative. The science of fibromyalgia. Mayo Clin Proc. 2011;86(9):907–11.

22. Vincent A, Lahr BD, Wolfe F, Clauw DJ, Whipple MO, Oh TH, et al. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. Arthritis Care Res. 2013;65(5):786–92.

23 Wolfe F, Brahlerbrabrahler E, Hinz A, Hauser W, Hauser H. Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. Arthritis Care Res. 2013;65(5):777–85.

24. Creed F. A review of the incidence and risk factors for fibromyalgia and chronic widespread pain in population-based studies. Pain. 2020;161(6): 1169–76.

25. Weir PT, Harlan GA, Nkoy FL, Jones SS, Hegmann KT, Gren LH, et al. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis. 2006;12(3):124–8.

26. Ursini F, Naty S, Grembiale RD. Fibromyalgia and obesity: the hidden link. Rheumatol Int. 2011;31(11):1403–8.

27 Queiroz LP. Worldwide epidemiology of fibromyalgia topical collection on fibromyalgia. Curr Pain Headache Rep. 2013;17:8.

28. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med. 2000;160(2):221–7.

29. Heidari F, Afshari M, Moosazadeh M. Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. Rheumatol Int. 2017;37(9):1527–39.

30. Rodriguez-Pintó I, Agmon-Levin N, Howard A, Shoenfeld Y. Fibromyalgia and cytokines. Immunol Lett. 2014;161(2):200–3.

31. Giovengo SL, Russell IJ, Larson AA. Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia. J Rheumatol. 1999;26(7):1564–9.

32. Vaerøy H, Helle R, Førre O, Kåss E, Terenius L. Elevated CSF levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis. Pain. 1988;32(1):21–6.

33. Larson AA, Giovengo SL, Russell IJ, Michalek JE. Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways. Pain. 2000;87(2):201–11.

34. Russell IJ, Orr MD, Littman B, Vipraio GA, Alboukrek D, Michalek JE, et al. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. Arthritis Rheum. 1994;37(11):1593–601.

35. Coskun BI. Role of inflammation in the pathogenesis and treatment of fibromyalgia. Rheumatol Int. 2019;39(5):781–91.

36. Theoharides TC, Tsilioni I, Bawazeer M. Mast cells, neuroinflammation and pain in fibromyalgia syndrome. Front Cell Neurosci. 2019;13:353.

37. Wang H, Moser M, Schiltenwolf M, Buchner M. Circulating cytokine levels compared to pain in patients with fibromyalgia—a prospective longitudinal study over 6 months. J Rheumatol. 2008;35(7):1366–70.

38. Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH. Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. Rheumatology. 2001;40(7):743–9.

39. Singh L, Kaur A, Bhatti MS, Bhatti R. Possible molecular mediators involved and mechanistic insight into fibromyalgia and associated co-morbidities. Neurochem Res. 2019;44(7):1517–32.

40 González-Vives S, Díaz-Marsá M, De-la Vega I, et al. Hypothalamic-pituitary axis response to a 0.25-MG dexamethasone test in women with fibromyalgia. Stress. 2020;23(3):284–9.

41. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. Psychoneuroendocrinology. 2005;30(10):1010–6.

42. Neyal M, Yimenicioglu F, Aydeniz A, Taskin A, Saglam S, Cekmen M, et al. Plasma nitrite levels, total antioxidant status, total oxidant status, and oxidative stress index in patients with tension-type headache and fibromyalgia. Clin Neurol Neurosurg. 2013;115(6):736–40.

43. Fatima G, Das SK, Mahdi AA. Oxidative stress and antioxidative parameters and metal ion content in patients with fibromyalgia syndrome: Implications in the pathogenesis of disease. Clin Exp Rheumatol. 2013;31:79.

44. Fatima G, Das SK, Mahdi AA. Some oxidative and antioxidative parameters and their relationship with clinical symptoms in women with fibromyalgia syndrome. Int J Rheum Dis. 2017;20(1):39–45.

45. Cordero MD, Díaz-Parrado E, Carrión AM, Alfonsi S, Sánchez-Alcazar JA, Bullón P, et al. Is inflammation a mitochondrial dysfunction-dependent event in fibromyalgia? Antioxid Redox Signal. 2013;18(7): 800–7.

46. Alcocer-Gómez E, Garrido-Maraver J, Bullón P, Marín-Aguilar F, Cotán D, Carrión AM, et al. Metformin and caloric restriction induce an AMPK-dependent restoration of mitochondrial dysfunction in fibroblasts from fibromyalgia patients. Biochim Biophys Acta Mol Basis Dis. 2015;1852(7):1257–67.

47. Mork PJ, Vasseljen O, Nilsen TIL. Association between physical exercise, body mass index, and risk of fibromyalgia: longitudinal data from the Norwegian Nord-Trøndelag health study. Arthritis Care Res. 2010;62(5):611–7.

48. Okifuji A, Hare BD. The association between chronic pain and obesity. J Pain Res. 2015;8: 399–408.

49. Üçeyler N, Burgmer M, Friedel E, Greiner W, Petzke F, Sarholz M, et al. Etiology and pathophysiology of fibromyalgia syndrome. Schmerz. 2017;31(3): 239–45.

50 Costantini A, Pala MI, Tundo S, Matteucci P. High-dose thiamine improves the symptoms of fibromyalgia. Case Rep. 2013;2013:bcr0013009019-bcr2013009019.

51. Ablin JN, Clauw DJ, Lyden AK, Ambrose K, Williams DA, Gracely RH, et al. Effects of sleep restriction and exercise deprivation on somatic symptoms and mood in healthy adults. Clin Exp Rheumatol. 2013;31(6 Suppl 79):S53–9.

52. McBeth J, Lacey RJ, Wilkie R. Predictors of new-onset widespread pain in older adults. Arthritis Rheumatol. 2014;66(3):757–67.

53 Lee C, Liptan G, Kantorovich S, Sharma M, Brenton A. Association of Catechol-O-methyltransferase single nucleotide polymorphisms, ethnicity, and sex in a large cohort of fibromyalgia patients. BMC Rheumatol. 2018;2:1.

54. Offenbaecher M, Bondy B, De Jonge S, Glatzeder K, Krüger M, Schoeps P, et al. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. Arthritis Rheum. 1999;42(11):2482–8.

55 Cohen H, Buskila D, Neumann L, Ebstein RP. Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5-HTTLPR) polymorphism, and relationship to anxiety-related personality traits. Arthritis Rheum. 2002;46:845–7.

56. Cohen H, Neumann L, Glazer Y, Ebstein RP, Buskila D. The relationship between a common catechol-*o*-methyltransferase (COMT) polymorphism val(158)Met and fibromyalgia. Clin Exp Rheumatol. 2009;27(5 Suppl 56):S51–6.

57. Finan PH, Zautra AJ, Davis MC, Lemery-Chalfant K, Covault J, Tennen H. COMT moderates the relation of daily maladaptive coping and pain in fibromyalgia. Pain. 2011;152(2):300–7.

58. Potvin S, Larouche A, Normand E, de Souza JB, Gaumond I, Grignon S, et al. DRD3 Ser9Gly polymorphism is related to thermal pain perception and modulation in chronic widespread pain patients and healthy controls. J Pain Off J Am Pain Soc. 2009;10(9):969–75.

59. Vargas-Alarcón G, Fragoso J-M, Cruz-Robles D, Vargas A, Martinez A, Lao-Villadóniga J-I, et al. Association of adrenergic receptor gene polymorphisms with different fibromyalgia syndrome domains. Arthritis Rheum. 2009;60(7):2169–73.

60. Aydin G, Başar MM, Keleş I, Ergün G, Orkun S, Batislam E. Relationship between sexual dysfunction and psychiatric status in premenopausal women with fibromyalgia. Urology. 2006;67(1): 156–61.

61 Mease P, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass JM, et al. Fibromyalgia syndrome module at OMERACT 9: domain construct. J Rheumatol. 2009;2009:2318–29.

62. Løge-Hagen JS, Sæle A, Juhl C, Bech P, Stenager E, Mellentin AI. Prevalence of depressive disorder among patients with fibromyalgia: systematic review and meta-analysis. J Affect Disord. 2019;245: 1098–105.

63. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Flub E, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017;76(2):318–28.

64. Chinn S, Caldwell W, Gritsenko K. Fibromyalgia pathogenesis and treatment options update. Curr Pain Headache Rep. 2016;20(4):1–10.

65. Jay GW, Barkin RL. Fibromyalgia. Dis Mon. 2015;61(3):66–111.

66 Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. Cochrane Database Syst Rev. 2018;2018:2.

67 Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for pain in fibromyalgia in adults. Cochrane Database Syst Rev. 2015;2017:5.

68. Häuser W, Petzke F, Üeyler N, Sommer C. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: A systematic review with meta-analysis. Rheumatology. 2011;50(3):532–43.

69 Walitt B, Urrútia G, Nishishinya MB, Cantrell SE, Häuser W. Selective serotonin reuptake inhibitors for fibromyalgia syndrome. Cochrane Database Syst Rev. 2015;2015:6.

70. Joelle-Thorpe I, Bonnie-Shum R, Andrew M, Philip J, Wiffen IG. Is combination pharmacotherapy effective for management of fibromyalgia in adults? A Cochrane review summary with commentary. Cochrane Database Syst Rev. 2020;20(3):297–300.

71. Hou WH, Wang TY, Kang JH. The effects of add-on non-invasive brain stimulation in fibromyalgia: a meta-analysis and meta-regression of randomized controlled trials. Rheumatol (Oxf). 2016;55(8): 1507–17.

72. Marlow NM, Bonilha HS, Short EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: a systematic review. Pain Pract. 2013;13(2):131–45.

73. Deus-Yela J, Soler MD, Pelayo-Vergara R, Vidal-Samso J. Estimulacion transcraneal por corriente directa en la fibromialgia: revision sistematica [Transcranial direct current stimulation for the treatment of fibromyalgia: a systematic review]. Rev Neurol. 2017;65(8):353–60.

74. Zhu CE, Yu B, Zhang W, Chen WH, Qi Q, Miao Y. Effectiveness and safety of transcranial direct current stimulation in fibromyalgia: a systematic review and meta-analysis. J Rehabil Med. 2017;49(1):2–9.

75. Yildiz S, Kiralp MZ, Akin A, et al. A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy. J Int Med Res. 2004;32(3):263–7.

76. Palzur E, Zaaroor M, Vlodavsky E, Milman F, Soustiel JF. Neuroprotective effect of hyperbaric oxygen therapy in brain injury is mediated by preservation of mitochondrial membrane properties. Brain Res. 2008;1221:126–33.

77. Kiralp MZ, Yildiz Ş, Vural D, Keskin I, Ay H, Dursun H. Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome. J Int Med Res. 2004;32(3):258–62.

78. Di Sabato F, Fusco BM, Pelaia P, Giacovazzo M. Hyperbaric oxygen therapy in cluster headache. Pain. 1993;52(2):243–5.

79. Kiralp MZ, Uzun G, Dinçer Ü, Sen A, Yildiz S, Tekin L, et al. A novel treatment modality for myofascial pain syndrome: hyperbaric oxygen therapy. J Natl Med Assoc. 2009;101(1):77–80.

80. Gu N, Niu JY, Liu WT, Sun YY, Liu S, Lv Y, et al. Hyperbaric oxygen therapy attenuates neuropathic hyperalgesia in rats and idiopathic trigeminal neuralgia in patients. Eur J Pain UK. 2012;16(8): 1094–105.

81. Joustra ML, Minovic I, Janssens KAM, Bakker SJL, Rosmalen JGM. Vitamin and mineral status in chronic fatigue syndrome and fibromyalgia syndrome: a systematic review and meta-analysis. PLoS ONE. 2017;12(4):e0176631.

82. Batista ED, Andretta A, de Miranda RC, Nehring J, Dos Santos PE, Schieferdecker ME. Food intake assessment and quality of life in women with fibromyalgia. Rev Bras Reumatol Engl Ed. 2016;56(2):105–10.

83. Vellisca MY, Latorre JI. Monosodium glutamate and aspartame in perceived pain in fibromyalgia. Rheumatol Int. 2014;34(7):1011–3.

84. Holton KF, Taren DL, Thomson CA, Bennett RM, Jones KD. The effect of dietary glutamate on fibromyalgia and irritable bowel symptoms. Clin Exp Rheumatol. 2012;30(6 Suppl 74):10–7.

85. Marum AP, Moreira C, Saraiva F, Tomas-Carus P, Sousa-Guerreiro C. A low fermentable oligo-di-mono saccharides and polyols (FODMAP) diet reduced pain and improved daily life in fibromyalgia patients. Scand J Pain. 2016;13:166–72.

86. Marum AP, Moreira C, Tomas-Carus P, Saraiva F, Guerreiro CS. A low fermentable oligo-di-monosaccharides and polyols (FODMAP) diet is a balanced therapy for fibromyalgia with nutritional and symptomatic benefits. Nutr Hosp. 2017;34(3): 667–74.

87. Arranz L-I, Canela M-Á, Rafecas M. Dietary aspects in fibromyalgia patients: results of a survey on food awareness, allergies, and nutritional supplementation. Rheumatol Int. 2012;32(9):2615–21.

88. Akbas A, Inanir A, Benli I, Onder Y, Aydogan L. Evaluation of some antioxidant enzyme activities (SOD and GPX) and their polymorphisms (MnSOD2 Ala9Val, GPX1 Pro198Leu) in fibromyalgia. Eur Rev Med Pharmacol Sci. 2014;18(8):1199–203.

89. Nazıroğlu M, Akkuş S, Soyupek F, Yalman K, Çelik Ö, Eriş S, et al. Vitamins C and E treatment combined with exercise modulates oxidative stress markers in blood of patients with fibromyalgia: a controlled clinical pilot study. Stress. 2010;13(6): 498–505.

90 Pagliai G, Giangrandi I, Dinu M, Sofi F, Colombini B. Nutritional interventions in the management of fibromyalgia syndrome. Nutrients. 2020;12:9.

91. Regland B, Forsmark S, Halaouate L, Matousek M, Peilot B, Zachrisson O, et al. Response to vitamin B12 and folic acid in myalgic encephalomyelitis and fibromyalgia. PLoS ONE. 2015;10(4):e0124648.

92. Obeid R, Kostopoulos P, Knapp J-P, Kasoha M, Becker G, Fassbender K, et al. Biomarkers of folate and vitamin B12 are related in blood and cerebrospinal fluid. Clin Chem. 2007;53(2):326–33.

93. Regland B, Andersson M, Abrahamsson L, Bagby J, Dyrehag LE, Gottfries CG. Increased concentrations of homocysteine in the cerebrospinal fluid in patients with fibromyalgia and chronic fatigue syndrome. Scand J Rheumatol. 1997;26(4):301–7.

94 de Carvalho JF, Silva DNF. Serum levels of vitamin B12 (cobalamin) in fibromyalgia. Rheumatol Int. 2016;36:741–2.

95. Chiu CK, Low TH, Tey YS, Singh VA, Shong HK. The efficacy and safety of intramuscular injections of methylcobalamin in patients with chronic non-specific low back pain: a randomised controlled trial. Singap Med J. 2011;52(12):868–73.

96. Zhang M, Han W, Hu S, Xu H. Methylcobalamin: a potential vitamin of pain killer. Neural Plast. 2013;2013:424651.

97. Hosseinzadeh H, Moallem SA, Moshiri M, Sarnavazi MS, Etemad L. Anti-nociceptive and anti-inflammatory effects of cyanocobalamin (vitamin B12) against acute and chronic pain and inflammation in mice. Arzneimittelforschung. 2012;62(7):324–9.

98. Ferreira I, Ortigoza Á, Moore P. Magnesium and malic acid supplement for fibromyalgia. Medwave. 2019;19(4):e7633.

99. Engen DJ, McAllister SJ, Whipple MO, Cha SS, Dion LJ, Vincent A, et al. Effects of transdermal magnesium chloride on quality of life for patients with fibromyalgia: a feasibility study. J Integr Med. 2015;13(5):306–13.

100. Andretta A, Dias Batista E, Madalozzo Schieferdecker ME, Rasmussen Petterle R, Boguszewski CL, Dos Santos PE. Relation between magnesium and calcium and parameters of pain, quality of life and depression in women with fibromyalgia. Adv Rheumatol (Lond, Engl). 2019;59(1):55.

101 Shin H-J, Na H-S, Do S-H. Magnesium and Pain. Nutrients. 2020;12:8.

102. Martínez-Rodríguez A, Rubio-Arias JÁ, Ramos-Campo DJ, Reche-García C, Leyva-Vela B, Nadal-Nicolás Y. Psychological and sleep effects of tryptophan and magnesium-enriched Mediterranean diet in women with fibromyalgia. Int J Environ Res Public Health. 2020;17:7.

103 Rezende RM, Gouveia-Pelúzio MDC, de Jesus-Silva F, et al. Does aerobic exercise associated with tryptophan supplementation attenuates hyperalgesia and inflammation in female rats with experimental fibromyalgia? PLoS ONE. 2019;14:2.

104. Tague SE, Clarke GL, Winter MK, McCarson KE, Wright DE, Smith PG. Vitamin D deficiency promotes skeletal muscle hypersensitivity and sensory hyperinnervation. J Neurosci. 2011;31(39): 13728–38.

105. Wu Z, Malihi Z, Stewart AW, Lawes CM, Scragg R. The association between vitamin D concentration and pain: a systematic review and meta-analysis. Public Health Nutr. 2018;21(11):2022–37.

106. Yong WC, Sanguankeo A, Upala S. Effect of vitamin D supplementation in chronic widespread pain: a systematic review and meta-analysis. Clin Rheumatol. 2017;36(12):2825–33.

107. Makrani AH, Afshari M, Ghajar M, Forooghi Z, Moosazadeh M. Vitamin D and fibromyalgia: a meta-analysis. Korean J Pain. 2017;30(4):250–7.

108. Ellis SD, Kelly ST, Shurlock JH, Hepburn ALN. The role of vitamin D testing and replacement in fibromyalgia: a systematic literature review. BMC Rheumatol. 2018;2:28.

109. Martins YA, Cardinali CAEF, Ravanelli MI, Brunaldi K. Is hypovitaminosis D associated with fibromyalgia? A systematic review. Nutr Rev. 2020;78(2): 115–33.

110. Beserra SR, Souza FIS, Sarni ROS, Pereira MMM. Association between low vitamin D levels and the greater impact of fibromyalgia. J Clin Med Res. 2020;12(7):436–42.

111 Karras S, Rapti E, Matsoukas S, Kotsa K. Vitamin D in fibromyalgia: a causative or confounding biological interplay? Nutrients. 2016;8:6.

112. D'Souza RS, Lin G, Oh T, et al. Fibromyalgia symptom severity and psychosocial outcomes in fibromyalgia patients with hypovitaminosis D: a prospective questionnaire study. Pain Med. 2020;21(12):3470–8.

113. Kasapoğlu Aksoy M, Altan L, Ökmen MB. The relationship between balance and vitamin 25(OH)D in fibromyalgia patients. Mod Rheumatol. 2017;27(5): 868–74.

114. Amin OA, Abouzeid SM, Ali SA, Amin BA, Alswat KA. Clinical association of vitamin D and serotonin levels among patients with fibromyalgia syndrome. Neuropsychiatr Dis Treat. 2019;15:1421–6.

115. Patrick RP, Ames BN. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. FASEB J. 2015;29(6):2207–22.

116. Wepner F, Scheuer R, Schuetz-Wieser B, et al. Effects of vitamin D on patients with fibromyalgia syndrome: a randomized placebo-controlled trial. Pain. 2014;155(2):261–8.

117. Mirzaei A, Zabihiyeganeh M, Jahed SA, Khiabani E, Nojomi M, Ghaffari S. Effects of vitamin D optimization on quality of life of patients with fibromyalgia: a randomized controlled trial. Med J Islam Repub Iran. 2018;32:29.

118. Yilmaz R, Salli A, Cingoz HT, Kucuksen S, Ugurlu H. Efficacy of vitamin D replacement therapy on patients with chronic nonspecific widespread musculoskeletal pain with vitamin D deficiency. Int J Rheum Dis. 2016;19(12):1255–62.

119. de Carvalho JF, da Rocha Araújo FAG, da Mota LMA, Aires RB, de Araujo RP. Vitamin D supplementation seems to improve fibromyalgia symptoms: preliminary results. Isr Med Assoc J. 2018;20(6):379–81.

120. Dogru A, Balkarli A, Cobankara V, Tunc SE, Sahin M. Effects of vitamin D therapy on quality of life in patients with fibromyalgia. Eurasian J Med. 2017;49(2):113–7.

121 Abou-Raya S, Abou-Raya A, Helmii M. THU0327 efficacy of vitamin D supplementation in the treatment of fibromyalgia: randomized controlled trial. Ann Rheum Dis. 2014;73(2):295.

122. Barrenetxe J, Delagrange P, Martínez JA. Physiological and metabolic functions of melatonin. J Physiol Biochem. 2004;60(1):61–72.

123. Huether G. The contribution of extrapineal sites of melatonin synthesis to circulating melatonin levels in higher vertebrates. Experientia. 1993;49(8): 665–70.

124. Acuña-Castroviejo D, Escames G, Venegas C, Díaz-Casado ME, Lima-Cabello E, López LC, et al. Extrapineal melatonin: sources, regulation, and potential functions. Cell Mol Life Sci. 2014;71(16): 2997–3025.

125. Sharafati-Chaleshtori R, Shirzad H, Rafieian-Kopaei M, Soltani A. Melatonin and human mitochondrial diseases. J Res Med Sci Off J Isfahan Univ Med Sci. 2017;22:2.

126. Jan JE, Espezel H, Appleion RE. The treatment of sleep disorders with melatonin. Dev Med Child Neurol. 1994;36(2):97–107.

127. Van Heukelom RO, Prins JB, Smits MG, Bleijenberg G. Influence of melatonin on fatigue severity in patients with chronic fatigue syndrome and late melatonin secretion. Eur J Neurol. 2006;13(1): 55–60.

128. Muszyńska B, Sułkowska-Ziaja K. Analysis of indole compounds in edible Basidiomycota species after thermal processing. Food Chem. 2012;132(1): 455–9.

129. Setyaningsih W, Saputro IE, Barbero GF, Palma M, García BC. Determination of melatonin in rice (*Oryza sativa*) grains by pressurized liquid extraction. J Agric Food Chem. 2015;63(4):1107–15.

130. Escrivá L, Manyes L, Barberà M, Martínez-Torres D, Meca G. Determination of melatonin in *Acyrthosiphon pisum* aphids by liquid chromatography-tandem mass spectrometry. J Insect Physiol. 2016;86: 48–53.

131. Yılmaz C, Kocadağlı T, Gökmen V. Formation of melatonin and its isomer during bread dough fermentation and effect of baking. J Agric Food Chem. 2014;62(13):2900–5.

132. Tan D-X, Zanghi BM, Manchester LC, Reiter RJ. Melatonin identified in meats and other food stuffs: potentially nutritional impact. J Pineal Res. 2014;57(2):213–8.

133 Aguilera Y, Herrera T, Benítez V, Arribas SM, López-de-Pablo AL, Esteban RM, et al. Estimation of scavenging capacity of melatonin and other antioxidants: contribution and evaluation in germinated seeds. Food Chem. 2015;170:203–11.

134. Nash MS, Osborne NN. Pertussis toxin-sensitive melatonin receptors negatively coupled to adenylate cyclase associated with cultured human and rat retinal pigment epithelial cells. Invest Ophthalmol Vis Sci. 1995;36(1):95–102.

135. Chneiweiss H, Glowinski J, Premont J. Mu and delta opiate receptors coupled negatively to adenylate cyclase on embryonic neurons from the mouse

striatum in primary cultures. J Neurosci Off J Soc Neurosci. 1988;8(9):3376–82.

136. Odagaki Y, Nishi N, Koyama T. Functional coupling of GABA(B) receptors with G proteins that are sensitive to *N*-ethylmaleimide treatment, suramin, and benzalkonium chloride in rat cerebral cortical membranes. J Neural Transm Vienna Austria. 2000;107(10):1101–16.

137. Ulugol A, Dokmeci D, Guray G, Sapolyo N, Ozyigit F, Tamer M. Antihyperalgesic, but not antiallodynic, effect of melatonin in nerve-injured neuropathic mice: possible involvements of the L-arginine-NO pathway and opioid system. Life Sci. 2006;78(14):1592–7.

138. Li S, Wang T, Wang R, Dai X, Chen Q, Li R. Melatonin enhances antinociceptive effects of delta-, but not mu-opioid agonist in mice. Brain Res. 2005;1043(1–2):132–8.

139. Dai X, Cui S, Li S, Chen Q, Wang R. Melatonin attenuates the development of antinociceptive tolerance to delta-, but not to mu-opioid receptor agonist in mice. Behav Brain Res. 2007;182(1):21–7.

140. Wang T, Li S-R, Dai X, Peng Y-L, Chen Q, Wang R. Effects of melatonin on orphanin FQ/nociceptin-induced hyperalgesia in mice. Brain Res. 2006;1085(1):43–8.

141. Golombek DA, Pévet P, Cardinali DP. Melatonin effects on behavior: possible mediation by the central GABAergic system. Neurosci Biobehav Rev. 1996;20(3):403–12.

142. Hussain SAR, Al-Khalifa II, Jasim NA, Gorial FI. Adjuvant use of melatonin for treatment of fibromyalgia. J Pineal Res. 2011;50(3):267–71.

143. Press J, Phillip M, Neumann L, Barak R, Segev Y, Abu-Shakra M, et al. Normal melatonin levels in patients with fibromyalgia syndrome. J Rheumatol. 1998;25(3):551–5.

144. Korszun A, Sackett-Lundeen L, Papadopoulos E, Brucksch C, Masterson L, Engelberg NC, et al. Melatonin levels in women with fibromyalgia and chronic fatigue syndrome. J Rheumatol. 1999;26(12):2675–80.

145. Wikner J, Hirsch U, Wetterberg L, Röjdmark S. Fibromyalgia—a syndrome associated with decreased nocturnal melatonin secretion. Clin Endocrinol (Oxf). 1998;49(2):179–83.

146. Tan D-X, Reiter RJ. Mitochondria: the birth place, battle ground and the site of melatonin metabolism in cells. Melatonin Res. 2019;2(1):44–66.

147. Stacchiotti A, Favero G, Rodella LF. Impact of melatonin on skeletal muscle and exercise. Cells. 2020;9(2):288.

148. Favero G, Bonomini F, Franco C, Rezzani R. Mitochondrial dysfunction in skeletal muscle of a fibromyalgia model: the potential benefits of melatonin. Int J Mol Sci. 2019;20:3.

149. Citera G, Arias MA, Maldonado-Cocco JA, Lázaro MA, Rosemffet MG, Brusco LI, et al. The effect of melatonin in patients with fibromyalgia: a pilot study. Clin Rheumatol. 2000;19(1):9–13.

150. de Zanette SAZ, Vercelino R, Laste G, Rozisky JRI, Schwertner A, Machado CB, et al. Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: a phase II, randomized, double-dummy, controlled trial. BMC Pharmacol Toxicol. 2014;15:40.

151. Castaño MY, Garrido M, Delgado-Adámez J, Martillanes S, Gómez MÁ, Rodríguez AB. Oral melatonin administration improves the objective and subjective sleep quality, increases 6-sulfatoxymelatonin levels and total antioxidant capacity in patients with fibromyalgia. J Appl Biomed. 2018;16(3):186–91.

152. Battino M, Fato R, Parenti-Castelli G, Lenaz G. Coenzyme Q can control the efficiency of oxidative phosphorylation. Int J Tissue React. 1990;12(3):137–44.

153. Cordero MD, Moreno-Fernández AM, deMiguel M, Bonal P, Campa F, Jiménez-Jiménez LM, et al. Coenzyme Q10 distribution in blood is altered in patients with fibromyalgia. Clin Biochem. 2009;42(7–8):732–5.

154. Haas RH. The evidence basis for coenzyme Q therapy in oxidative phosphorylation disease. Mitochondrion. 2007;7:136–45.

155. Montero R, Sánchez-Alcázar JA, Briones P, Hernández ÁR, Cordero MD, Trevisson E, et al. Analysis of coenzyme Q10 in muscle and fibroblasts for the diagnosis of CoQ10 deficiency syndromes. Clin Biochem. 2008;41(9):697–700.

156. Land JM, Heales SJR, Duncan AJ, Hargreaves IP. Some observations upon biochemical causes of ataxia and a new disease entity ubiquinone, CoQ10 deficiency. Neurochem Res. 2007;32(4–5):837–43.

157. Alcocer-Gómez E, Cano-García FJ, Cordero MD. Effect of coenzyme Q10 evaluated by 1990 and 2010 ACR diagnostic criteria for fibromyalgia and SCL-90-R: four case reports and literature review. Nutrition. 2013;29(11–12):1422–5.

158. Cordero MD, Alcocer-Gómez E, De Miguel M, Cano-García FJ, Luque CM, Fernández-Riejo P, et al. Coenzyme Q10: a novel therapeutic approach for fibromyalgia? Case series with 5 patients. Mitochondrion. 2011;11(4):623–5.

159. Lister RE. An open, pilot study to evaluate the potential benefits of coenzyme Q10 combined with Ginkgo biloba extract in fibromyalgia syndrome. J Int Med Res. 2002;30(2):195–9.

160. Cordero MD, Alcocer-Gómez E, De Miguel M, Culic O, Carrión AM, Alvarez-Suarez JM, et al. Can coenzyme Q10 improve clinical and molecular parameters in fibromyalgia? Antioxid Redox Signal. 2013;19(12):1356–61.

161. Cordero MD, Cotán D, del-Pozo-Martín Y, Carrión AM, de-Miguel M, Bullón P et al. (2012) Oral coenzyme Q10 supplementation improves clinical symptoms and recovers pathologic alterations in blood mononuclear cells in a fibromyalgia patient. Nutrition 2012; 28(11–12):1200–3.

162. Díaz-Castro J, Guisado R, Kajarabille N, García C, Guisado IM, de Teresa C, et al. Coenzyme Q10 supplementation ameliorates inflammatory signaling and oxidative stress associated with strenuous exercise. Eur J Nutr. 2012;51(7):791–9.

163. Wang ZQ, Porreca F, Cuzzocrea S, Galen K, Lightfoot R, Masini E, et al. A newly identified role for superoxide in inflammatory pain. J Pharmacol Exp Ther. 2004;309(3):869–78.

164. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol. 2012;13(4):251–62.

165. Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. Brain Behav Immun. 2014;38:1–12.

166. Tillisch K. The effects of gut microbiota on CNS function in humans. Gut Microbes. 2014;5(3):404–10.

167. Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain–gut–enteric microbiota axis. Nat Rev Gastroenterol Hepatol. 2009;6(5):306–14.

168. Romijn JA, Corssmit EP, Havekes LM, Pijl H. Gut–-brain axis. Curr Opin Clin Nutr Metab Care. 2008;11(4):518–21.

169. Triadafilopoulos G, Simms RW, Goldenberg DL. Bowel dysfunction in fibromyalgia syndrome. Dig Dis Sci. 1991;36(1):59–64.

170. Riedl A, Schmidtmann M, Stengel A, Goebel M, Wisser A-S, Klapp BF, et al. Somatic comorbidities of irritable bowel syndrome: a systematic analysis. J Psychosom Res. 2008;64(6):573–82.

171. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology. 2002;122(4):1140–56.

172. Sperber AD, Atzmon Y, Neumann L, Weisberg I, Shalit Y, Abu-Shakrah M, et al. Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications. Am J Gastroenterol. 1999;94(12):3541–6.

173. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med. 2001;134(9 Pt 2):868–81.

174. Butt HL, Dunstan RH, McGregor NR, Roberts TK. Bacterial colonosis in patients with persistent fatigue. In: Proceedings of the AHMF international clinical and scientific conference; 2001. p. 1–2.

175. Sheedy JR, Wettenhall REH, Scanlon D, Gooley PR, Lewis DP, McGregor N, et al. Increased d-lactic acid intestinal bacteria in patients with chronic fatigue syndrome. Vivo Athens Greece. 2009;23(4):621–8.

176. Pimentel M, Wallace D, Hallegua D, Chow E, Kong Y, Park S, et al. A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing. Ann Rheum Dis. 2004;63(4):450–2.

177. Clos-Garcia M, Andrés-Marin N, Fernández-Eulate G, Abecia L, Lavín JL, van Liempd S, et al. Gut microbiome and serum metabolome analyses identify molecular biomarkers and altered glutamate metabolism in fibromyalgia. EBioMedicine. 2019;46:499–511.

178. Rao AV, Bested AC, Beaulne TM, Katzman MA, Iorio C, Berardi JM, et al. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. Gut Pathog. 2009;1(1):6.

179. Groeger D, O'Mahony L, Murphy EF, Bourke JF, Dinan TG, Kiely B, et al. Bifidobacterium infantis 35624 modulates host inflammatory processes beyond the gut. Gut Microbes. 2013;4(4):325–39.

180. Roman P, Carrillo-Trabalón F, Sánchez-Labraca N, Cañadas F, Estévez AF, Cardona D. Are probiotic treatments useful on fibromyalgia syndrome or chronic fatigue syndrome patients? A systematic review. Benef Microbes. 2018;9(4):603–11.

181. Pamuk GE, Pamuk ON, Set T, Harmandar O, Yeşil N. An increased prevalence of fibromyalgia in iron deficiency anemia and thalassemia minor and

associated factors. Clin Rheumatol. 2008;27(9): 1103–8.

182. Ortancil O, Sanli A, Eryuksel R, Basaran A, Ankarali H. Association between serum ferritin level and fibromyalgia syndrome. Eur J Clin Nutr. 2010;64(3): 308–12.

183. Dowling P, Klinker F, Amaya F, Paulus W, Liebetanz D. Iron-deficiency sensitizes mice to acute pain stimuli and formalin-induced nociception. J Nutr. 2009;139(11):2087–92.

184. Mader R, Koton Y, Buskila D, Herer P, Elias M. Serum iron and iron stores in non-anemic patients with fibromyalgia. Clin Rheumatol. 2012;31(4): 595–9.

185. Russell IJ, Vaeroy H, Javors M, Nyberg F. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. Arthritis Rheum. 1992;35(5):550–6.

186. Legangneux E, Mora JJ, Spreux-Varoquaux O, Thorin I, Herrou M, Alvado G, et al. Cerebrospinal fluid biogenic amine metabolites, plasma-rich platelet serotonin and [3H]imipramine reuptake in the primary fibromyalgia syndrome. Rheumatology. 2001;40(3):290–6.

187. Boomershine CS, Koch TA, Morris D. A blinded, randomized, placebo-controlled study to investigate the efficacy and safety of ferric carboxymaltose in iron-deficient patients with fibromyalgia. Rheumatol Ther. 2017;5(1):271.