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Higher CRP levels may play a role in fibromyalgia

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ORIGINAL ARTICLES

Inflammatory Markers in the Diagnosis of Fibromyalgia

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Higher CRP levels may play a role in fibromyalgia

Table 1. Demographic and clinical characteristic of the study patients according to their group

Variables (mean ± standard deviation)	Control (n=76)	Fibromyalgia (n=75)	P value*
Sex, Female (n)	69 (90.8%)	67 (89.3%)	0.765
Mean age (years)	50.5 ± 10.6	56.7 ± 14.3	0.003
Lymphocytes (10 ³ u/l)	2.38 ± 0.79	2.06 ± 0.72	0.014
Neutrophils (10 ³ u/l)	5.16 ± 2.20	5.37 ± 3.12	0.921
Platelets (10 ³ u/l)	231 ± 68	265 ± 81	0.003
Red cell distribution width (%)	13.83 ± 1.19	13.98 ± 1.01	0.219
Mean platelet value	8.58 ± 0.96	8.94 ± 1.43	0.316
Neutrophil-lymphocytes ratio	2.48 ± 1.49	2.99 ± 2.81	0.118
Platelet-lymphocyte ratio	107.6 ± 45.3	143.6 ± 67.9	< 0.001
C-reactive protein (mg/l)	2.7 ± 2.3	17.6 ± 33.7	< 0.001

*Bold indicates significance

Higher CRP levels may play a role in fibromyalgia

- Our main finding shows statistically significant higher CRP levels, which indicate inflammation, might play a role in the pathogenesis of FMS.
- Our results are consistent with the results of previous small studies that showed similar findings showing that FMS is an inflammatory disease [17].
- In a cross-sectional study of a large population in the United States, CRP serum levels showed a positive association with FMS, which remained significant after adjustment for multiple variants; however, body mass index (BMI) and co-morbidity substantially attenuated this relationship [17].
 - We excluded patients with co-morbidities but unfortunately, we did not examine BMI

Medical Cannabis for Fibromyalgia

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A Systematic Review of Fibromyalgia and Recent Advancements in Treatment: Is Medicinal Cannabis a New Hope?

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Medical Cannabis for Fibromyalgia

- Although the studies reviewed in this article suggest that medical cannabis is a safe and effective treatment for fibromyalgia pain
- There were several limitations:
 - Dosage
 - Length of treatment
 - Adverse effects
 - Long-term follow-up
 - Dependence
 - Needs further investigation.

A total of 363 articles were retrieved after title screening. A total of 250 less relevant articles were excluded, and 163 articles were retained.

A total of 25 more articles were excluded after reading the full text, assessing the quality appraisal and relevance related to the research question. Finally, **22 articles were retrieved for study**

Medical Cannabis for Fibromyalgia

- The most important pathological mechanism is the alteration of central pathways or central sensitization with amplification of pain perception. The hypothalamic-pituitary-adrenal (HPA) axis is considered to play an important role in the establishment of central sensitization¹⁻²
- One interesting hypothesis favors the role of the thalamic mast cell that may contribute to the release of histamine, interleukin-1 beta, IL-6, tumor necrosis factor (TNF), and calcitonin gene-related peptide, which stimulates nociceptive neurons directly or indirectly by stimulation of microglia¹.
- The evidence that supports the role of mast cells in fibromyalgia states that CCL1 (eotaxin1) and CCL2 (eotaxin-2), which function as potent chemoattractants for inflammatory cells, were found to be elevated in patients with FMS².

¹Bazzichi L, Giacomelli C, Consensi A, Giorgi V, Batticciotto A, Di Franco M, Sarzi-Puttini P: One year in review 2020: fibromyalgia. Clin Exp Rheumatology. 2020, 38:3-8.

²Banfi G, Diani M, Pigatto PD, Reali E: T cell subpopulations in the physiopathology of fibromyalgia: evidence and perspectives. Int J Mol Sci. 2020, 21:1186. 10.3390/ijms21041186

Medical Cannabis for Fibromyalgia

- In one experimental study designed to examine the effect of adding medical cannabis to analgesic treatment, which consisted of 38 patients treated for three months with standard analgesic therapy with minor improvement in the symptoms, treated with medical cannabis therapy for a minimum of six months
- This resulted in higher improvement in all patient-reported outcomes (PROs), which included Fibromyalgia Impact Questionnaire (FIQ), visual analog scale (VAS), Oswestry Disability Index (ODI), and lumbar range of motion (ROM), which was recorded using the modified Schober's test¹.

¹Yassin M, Oron A, Robinson D: Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: an observational cross-over single centre study. Clin Exp Rheumatol. 2019, 37:13-20. 10.21767/2471-982X.100016

Medical Cannabis for Fibromyalgia

- One study¹ consisting of 367 patients conducted to investigate the safety and efficacy of medical cannabis in fibromyalgia was conducted on patients who were willing to answer the questionnaire in a specialized medical cannabis clinic between 2015 and 2017.
- It concluded that medical cannabis appears to be a safe and effective alternative for the treatment of fibromyalgia symptoms with certain limitations like standardization of treatment compounds and regimens, which require more research.
- This study included patients with six months follow-up and the response rate was 70.8%.
- **The pain intensity reduced from a median of 9.0 at baseline to 5.0 on a pain scale 0-10 ($p < 0.001$), and 194 patients (81.1%) achieved treatment response.**
- The most common adverse effects were mild and included dizziness, dry mouth, and gastrointestinal symptoms.

¹Sagy I, Bar-Lev Schleider L, Abu-Shakra M, Novack V: Safety and efficacy of medical cannabis in fibromyalgia. J Clin Med. 2019, 8:807. 10.3390/jcm8060807

Medical Cannabis for Fibromyalgia

- With previous knowledge on two different compounds (Bedrocan and Bediol), another study carried out to study further outcomes, included 102 FM patients to assess any clinical improvement following the addition of medical cannabis treatment (MCT) to the stable (\geq three months) standard analgesic treatment of FM patients.
- Patients were prescribed two oil-diluted cannabis extracts: Bedrocan (22% THC, <1% CBD), and Bediol (6.3% THC, 8% CBD). FM severity was periodically assessed using the Fibromyalgia Impact Questionnaire (FIQ), Fibromyalgia Assessment Scale (FAS), Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score, Pittsburgh Sleep Quality Index (PSQI), and Zung Depression and Anxiety Scales. During the study, patients were allowed to reduce or stop their concomitant analgesic therapy.
- Finally, **50% showed a moderate improvement in anxiety and depression**; besides, **analgesic treatment was reduced or suspended in 47% of the patients**. In general, only one-third experienced mild adverse events. Overall, it showed that adjunctive MCT offers a possible clinical advantage in FM patients [22].

Bedrocan (www.bedrocan.com) produces five cannabis products or plant varieties for [medicine development](#), patients and [clinical use](#). Each cannabis product is standardized according to pharmaceutical standards with a defined active ingredient composition. Every stage of the manufacturing process is [GMP-certified](#) (good manufacturing practice). GMP is a requirement of the pharmaceutical industry and it ensures consistency in active ingredients, which can affect a medicine's safety and efficacy. Our cannabis products are independently tested for desired properties by a [specialised laboratory](#). – *Only available to medical providers for RESEARCH in the USA.*

Medical Cannabis for Fibromyalgia

- Recently a retrospective, open-label case series consisting of 38 patients was conducted to study the efficacy and adverse events (AEs) of short- and long-term Medical Cannabis (MC) treatment for FM concluded that MC may be used as an alternative treatment for patients with FMS who are unresponsive to conventional therapy.
 - However, its application may be limited by the incidence of non-serious adverse effects.
- The study was conducted for 12 months with follow-up at 1, 3, and 12 months.
- The results were interpreted based on certain scales including Numerical Rating Scale (NRS), Oswestry Disability Index (ODI), Hospital Anxiety and Depression Scale (HADS), Widespread Pain Index (WPI), and Severity Score (SYS).
- The most common side effects were mental confusion, dizziness, nausea/vomiting, and restlessness/irritation¹.

¹Mazza M: Medical cannabis for the treatment of fibromyalgia syndrome: a retrospective, open-label case series. J Cannabis Res. 2021, 3:4. 10.1186/s42238-021-00060-6



Spinal Cord Resting State Activity in Individuals With Fibromyalgia Who Take Opioids

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Chronic pain coincides with myriad functional alterations throughout the brain and spinal cord. While spinal cord mechanisms of chronic pain have been extensively characterized in animal models and *in vitro*, to date, research in patients with chronic pain has focused only very minimally on the spinal cord. Previously, spinal cord functional magnetic resonance imaging (fMRI) identified regional alterations in spinal cord activity in patients

Spinal Cord activity normalizes in Fibro patients on opioids

- Across patient groups, self-reported fatigue correlated with regional differences in spinal cord activity. – More fatigue, increased activity
- Additionally, spinal cord functional connectivity and graph metrics did not differ among groups.
- **Our findings suggest that, contrary to our main hypothesis, patients with fibromyalgia who take opioids do not have greater alterations in regional spinal cord activity.**
- Thus, regional spinal cord activity may be less imbalanced in patients taking opioids compared to patients not taking opioids.



Altered Pain in the Brainstem and Spinal Cord of Fibromyalgia Patients During the Anticipation and Experience of Experimental Pain

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Pain is altered in the brain and spinal cord of fibromyalgia patients

- Evidence suggests that FM involves altered neural processes in the central nervous system and neuroimaging methods such as functional magnetic resonance imaging (fMRI) are used to reveal these underlying alterations.
- Functional magnetic resonance imaging data from 15 women with FM and 15 healthy controls were obtained in the cervical spinal cord and brainstem at 3 tesla using previously established methods. In order to investigate differences in pain processing in these groups, participants underwent trials in which they anticipated and received a predictable painful stimulus, randomly interleaved with trials with no stimulus.

Pain is altered in the brain and spinal cord of fibromyalgia patients

- Differences in functional connectivity between the groups were investigated by means of structural equation modeling.
- The results demonstrate significant differences in brainstem/spinal cord network connectivity between the FM and control groups which also correlated with individual differences in pain responses.
- The regions involved in these differences in connectivity included the LC, hypothalamus, PAG, and PBN, which are known to be associated with autonomic homeostatic regulation, including fight or flight responses.

Pain is altered in the brain and spinal cord of fibromyalgia patients

- In the Expectation period, group differences in connectivity involved mainly signaling from the hypothalamus to brainstem areas such as the spinal cord to the thalamus.
- **This may indicate that a component of fibromyalgia pain is altered pain modulation during the anticipation of pain.**
- As we demonstrated in our previous study, pain modulation includes a continuous component which is present before a painful stimulus is applied and may contribute to readying spinal cord areas to receive incoming nociceptive signals¹

¹Stroman PW, Ioachim G, Powers JM, Staud R, Pukall C. Pain processing in the human brainstem and spinal cord before, during, and after the application of noxious heat stimuli. *Pain*. (2018) 159:2012–20. doi: 10.1097/j.pain.0000000000001302

Pain is altered in the brain and spinal cord of fibromyalgia patients

- Descending pain regulation is altered in fibromyalgia during noxious stimulation, as the primary differences in connectivity involve the PAG-RVM-spinal cord descending pain modulation pathway¹
- The areas involved in these differences may therefore indicate that this altered descending regulation may have a contribution from altered autonomic signaling.
- While FM pain has been associated with autonomic dysfunction in previous behavioral studies ²⁻⁴, this is the first study to show evidence of this link that is supported by fMRI data

¹Millan MJ. Descending control of pain. *Prog Neurobiol.* (2002) 66:355– 474. doi: 10.1016/S0301-0082(02)00009-6

²Kulshreshtha P, Gupta R, Yadav RK, Bijlani RL, Deepak KK. A comprehensive study of autonomic dysfunction in the fibromyalgia patients. *Clin Auton Res.* (2012) 22:117–22. doi: 10.1007/s10286-011-0150-6

³Schmidt-Wilcke T, Diers M. New Insights into the Pathophysiology and Treatment of Fibromyalgia. *Biomedicines.* (2017) 5:22. doi: 10.3390/biomedicines5020022

⁴ Casale R, Sarzi-Puttini P, Botto R, Alciati A, Batticciotto A, Marotto D, et al. Fibromyalgia and the concept of resilience. *Clin Exp Rheumatol.* (2019) 37 (Suppl 116):105–13.

Pain is altered in the brain and spinal cord of fibromyalgia patients

- The authors showed that maladaptive emotional regulation in response to acute pain may contribute to depressed mood and enhanced pain catastrophizing (but not anxiousness), and in turn mediate altered pain responses.¹
- Our results align with this idea as we found that women with fibromyalgia had higher BDI and PCS scores than the controls but not STAI scores

¹Koechlin H, Coakley R, Senechter N, Werner D, Kossowsky U. The role of emotion regulation in chronic pain: A systematic literature review. J Psychosom Res. (2018) 107:38–45. doi: 10.1016/j.jpsychores.2018.02.002

Pain is altered in the brain and spinal cord of fibromyalgia patients

- People with fibromyalgia have more difficulty regulating emotions, and this predicted heightened pain responses depending on their coping strategies¹
- Our fibromyalgia group had significantly higher pain catastrophizing scores² than the healthy control group, a measure which takes into account in part how people think about and attend to their pain.
- The altered pain experienced by the fibromyalgia participants is likely due to alterations in a convergence of autonomic regulation and pain modulation systems.

¹Trucharte A, Leon L, Castillo-Parra G, Magan I, Freitas D, Redondo M. Emotional regulation processes: influence on pain and disability in fibromyalgia patients. *Clin Exp Rheumatol.* (2020) 38 (Suppl 123):40–6.

²Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess.* (1995) 7:524– 32. doi: 10.1037/1040-3590.7.4.524

Pain is altered in the brain and spinal cord of fibromyalgia patients

- Motivational-affective components of pain processing and autonomic control are closely interlinked and have been shown to contribute to altered pain responses in the brain.
- Based on this and the evidence that maladaptive emotional regulation (an affective component of pain processing) can lead to altered pain in fibromyalgia ¹⁻²
- It is possible that our results show the underlying neural basis of these effects at the level of the brainstem and spinal cord.

¹Koechlin H, Coakley R, Schechter N, Werner C, Kossowsky J. The role of emotion regulation in chronic pain: A systematic literature review. *J Psychosom Res.* (2018) 107:38–45. doi: 10.1016/j.jpsychores.2018.02.002

²Trucharte A, Leon L, Castillo-Parra G, Magan I, Freites D, Redondo M. Emotional regulation processes: influence on pain and disability in fibromyalgia patients. *Clin Exp Rheumatol.* (2020) 38 (Suppl 123):40–6.

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

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Nutrient Supplementation in Fibromyalgia

- 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.
- 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.

Nutrient Supplementation in Fibromyalgia

There is a strong consensus that the following have a strong association with FM

- **Biological factors**
 - Inflammatory rheumatic disease, gene polymorphisms, vitamin D deficiency, thiamine deficiency)
- **Lifestyle factors**
 - Smoking, poor diet, sedentary lifestyle, and being overweight
- **Psychological factors**
 - Physical and/or sexual abuse in childhood, sexual violence in adulthood, and depressive disorders.

Nutrient Supplementation in Fibromyalgia

- 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].
- There are two main classes of pharmacotherapeutics prescribed for FM:
 - Anti-epileptic drugs (AEDs)
 - Pregabalin
 - The antidepressants utilized are:
 - Tricyclic antidepressants (TCAs)
 - Selective serotonin reuptake inhibitor (SSRIs)
 - Serotonin-norepinephrine reuptake inhibitor (SNRIs)
 - Pregabalin, duloxetine, and milnacipran are the only FDA-approved drug treatments for FM, and all other treatment is considered off-label [64, 65].

Nutrient Supplementation in Fibromyalgia

- 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]
- 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].

Nutrient Supplementation in Fibromyalgia

- 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].
- 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].

Non-Invasive Therapies for Fibromyalgia

- Non-invasive neurostimulation therapies have been studied as therapeutic options to reduce pain perception in FM.
 - Transcranial direct current stimulation (tDCS)
 - Repetitive transcranial magnetic stimulation (rTMS)
 - 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].

Oxidative Stress and Free Radicals in Fibromyalgia

- 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 (CoQ10)** [45, 46].

CoQ10 - Supplementation

- In a review of multiple experimental studies, melatonin supplementation led to an improvement in several outcome measures of FM:
 - Disease impact
 - Sleep quality
 - Pain level
 - Tender point count.
- Contrarily, the studies did not find conclusive evidence that melatonin improves anxiety, fatigue, or depression in FM patients [142, 149–151].

CoQ10 - Mechanism

- The mechanisms of FM symptomatic improvement after CoQ10 supplementation are not entirely understood, but several mechanisms are proposed.
 - One relates to the role of CoQ10 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 CoQ10 deficiency may have a significant role in symptom severity, and patients have shown improvement following CoQ10 supplementation [153, 158–161].
 - CoQ10 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, CoQ10 has been suggested to have antioxidant properties [153].
 - Various stressors may affect CoQ10 levels in the body, but it is known that myopathies feature reduced CoQ10 levels
 - Whether as a cause or effect of the myopathy remains to be determined [154].

CoQ10 - Mechanism

- CoQ10 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 CoQ10 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 CoQ10 has in FM [157, 160].
- The effects of CoQ10 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.

Hyperbaric Oxygen Therapy in Fibromyalgia

- 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 antiinflammatory response [75, 76].

Dietary changes in Fibromyalgia

- 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].

Magnesium Supplementation

- 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]
- 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.
 - Central sensitization is directly related to the increased intracellular calcium that is a result of the excitation of the NMDA receptor.

Magnesium Supplementation

- 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].

Tryptophan-Magnesium Supplementation

- 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].

Vitamin C & E Supplementation

- **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].

B12 and B9 Supplementation

- 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.**
 - 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**
 - Both vitamins B12 and B9 are cofactors in the metabolism of homocysteine (HCY).
 - 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
 - **Increased amounts of vitamins B12 and B9 may lower the CSF-HCY concentration [92].**
 - Though this research is promising, other studies have failed to prove a connection between B12 deficiency and FM [94].

Vitamin D - Supplementation

- FOR
 - Vitamin D has been shown to influence nociceptive innervation on skeletal muscle, resulting in hyperinnervation and hypersensitivity to musculoskeletal pain when deficient [104]
 - 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].
- AGANIST
 - 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].
 - A recent crosssectional 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].

Vitamin D - Mechanism

- 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.
- 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.

Melatonin Supplementation

- 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].
- 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].

Melatonin - Mechanism

- 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:
 - Gi-coupled melatonin receptors,
 - Gicoupled opioid I-receptors
 - Gammaaminobutyric-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].

Probiotic - Supplementation

- 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].
- 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].
- Of the available evidence, numerous studies of conditions closely related to FM, such as IBS and CFS, demonstrated inconsistent results between studies [180].
- 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.

Iron - Supplementation

- 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].
- 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].

Iron - Mechanism

- 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].
- 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].
- 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].



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Please contact me with any questions

Chris J Kottenstette, PA-C,

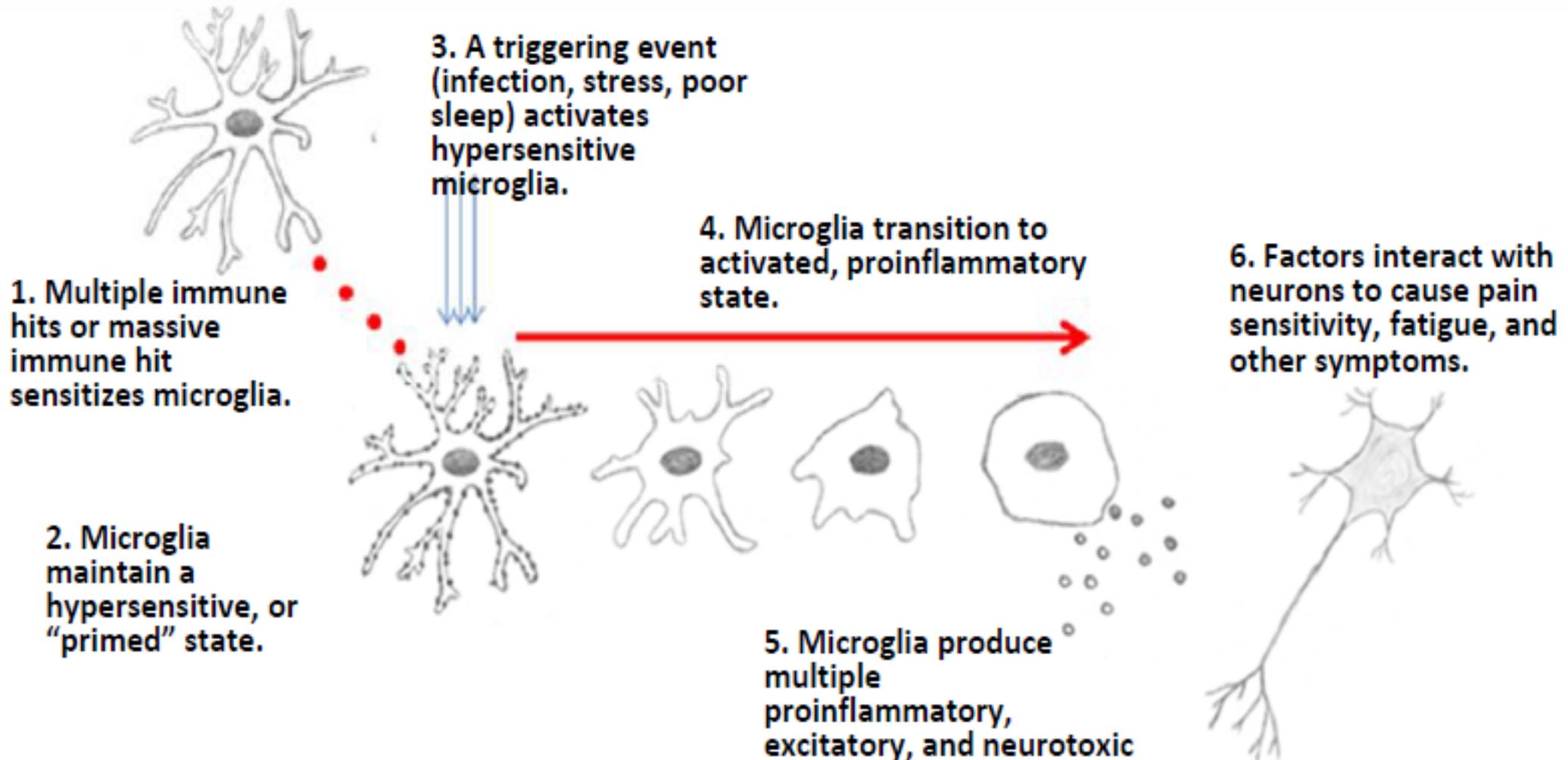
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Proposed Pathophysiology



Driving Force: Microglia

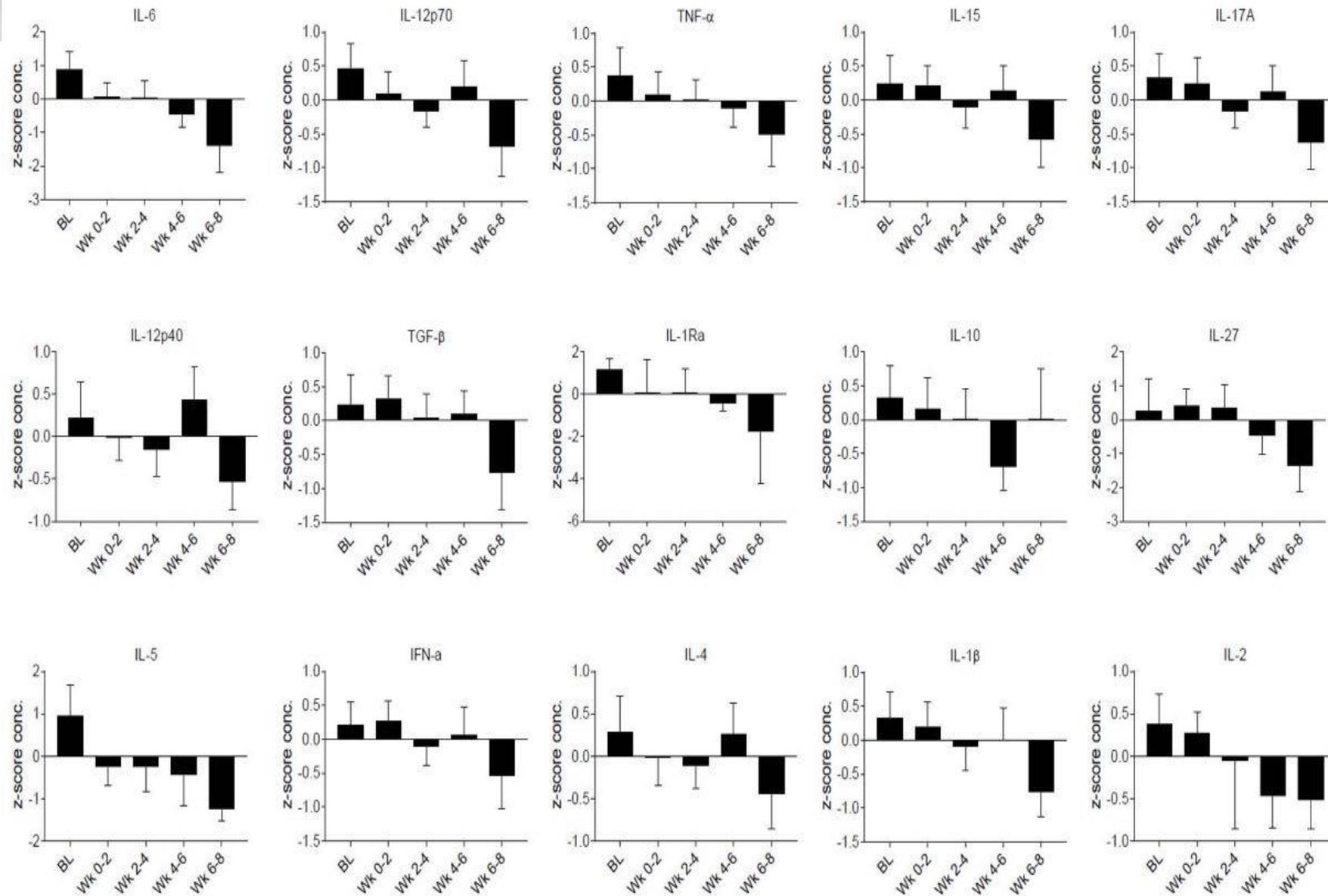
- Microglia cells are the immune cells of the central nervous system and consequently play important roles in brain infections and inflammation.

- <https://pubmed.ncbi.nlm.nih.gov/22613055/>

Low Dose Naltrexone

- Naltrexone is approved to treat opioid drug dependency and alcohol abuse
- Research has shown that using very low doses can improve symptoms of fibromyalgia

Cytokine Response to Naltrexone



Barriers to treatment

- Chronic opioid use for other conditions
- Socioeconomic status
- Reluctance to use non-FDA approved medication
- Fear of being labeled as a drug addict

Clinical Implications

- Constitutional symptoms
 - Low body temperature
 - Fatigue
 - Poor sleep
 - Depressed mood
 - Lack of interest

Side effects

Nausea

Vivid dreams

Increased depression

Allergy

Articles

- https://www.medscape.com/viewarticle/926611#vp_2
- <https://pubmed.ncbi.nlm.nih.gov/23359310/>
- <https://pubmed.ncbi.nlm.nih.gov/28325149/>
- <https://clinicaltrials.gov/ct2/show/NCT04270877>