Pain Ther
https://doi.org/10.1007/s40122-024-00641-2

REVIEW

Neuronutritional Approach to Fibromyalgia Management: A Narrative Review

Anastasiia Badaeva · Alexey Danilov · Anastasiia Kosareva · Mariia Lepshina · Viacheslav Novikov · Yulia Vorobyeva · Andrey Danilov

Received: June 7, 2024 / Accepted: July 12, 2024

ABSTRACT

Fibromyalgia (FM) is a complex and common syndrome characterized by chronic widespread pain, fatigue, sleep disturbances, and various functional symptoms without clear structural or pathological causes. Affecting approximately 1–5% of the global population, with a higher prevalence in women, FM significantly impacts patients' quality of life, often leading to considerable healthcare costs and loss of productivity. Despite its prevalence, the etiology of FM remains elusive, with genetic, environmental, and psychological factors, including nutrition, being implicated. Currently, no universally accepted treatment guidelines exist, and management strategies are often symptomatic. This narrative review explores the potential of a neuronutritional approach to FM management. It synthesizes existing research on the relationship between FM and nutrition, suggesting that dietary interventions could be a promising complementary treatment strategy. Various nutritional interventions, including vitamin D, magnesium, iron, and probiotics supplementation, have shown potential in reducing FM symptoms, such as chronic pain, anxiety, depression, cognitive dysfunction, sleep disturbances, and gastrointestinal issues. Additionally, weight loss has been associated with reduced inflammation and improved quality of life in FM patients. The review highlights the anti-inflammatory benefits of plant-based diets and the low-FODMAPs diet, which have shown promise in managing FM symptoms and related gastrointestinal disorders. Supplements such as vitamin D, magnesium, vitamin B12, coenzyme Q10, probiotics, omega-3 fatty acids, melatonin, S-adenosylmethionine, and acetyl-L-carnitine

A. Badaeva (✉)
Department for Pathological Physiology, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), 119991 Moscow, Russia
e-mail: badaeva_a_v@staff.sechenov.ru

A. Danilov · A. Kosareva · M. Lepshina · V. Novikov · Y. Vorobyeva · A. Danilov
Department for Nervous Diseases, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), 119991 Moscow, Russia
e-mail: danilov_a_b_2@staff.sechenov.ru

A. Kosareva
e-mail: drkosareva@yandex.com

M. Lepshina
e-mail: lepshina_m_m@student.sechenov.ru

V. Novikov
e-mail: novikov_v_n@student.sechenov.ru

Y. Vorobyeva
e-mail: vorobeva_yu_d@staff.sechenov.ru

A. Danilov
e-mail: andreidanilov@mail.ru

Published online: 23 July 2024

are discussed for their potential benefits in FM management through various mechanisms, including anti-inflammatory effects, modulation of neurotransmitters, and improvement of mitochondrial function. In conclusion, this review underscores the importance of considering neuronutrition as a holistic approach to FM treatment, advocating for further research and clinical trials to establish comprehensive dietary guidelines and to optimize management strategies for FM patients.

Keywords: Chronic pain; Dietary interventions; Fibromyalgia; Inflammation; Neuronutrition; Nutritional supplements; Quality of life

Key Summary Points

Nutritional interventions, such as vitamin D, magnesium, vitamin B12, coenzyme Q10, probiotics, omega-3 fatty acids, melatonin, S-adenosylmethionine, acetyl-L-carnitine, and curcumin supplementation have shown potential in reducing fibromyalgia (FM) symptoms.

They target different mechanisms from energy to neurotransmitter metabolism involved in FM pathogenesis.

Additionally, weight loss and plant-based dietary interventions have been associated with reduced inflammation and improved quality of life in FM patients.

Research on a neuronutritional approach to FM treatment is needed to establish comprehensive dietary guidelines and to optimize management strategies for FM patients.

INTRODUCTION

Fibromyalgia (FM) is one of the most common causes of chronic widespread pain. This is a complex syndrome that includes the following symptoms besides pain: fatigue, sleep disturbances, and functional symptoms—medical conditions with no structural or pathological cause [1]. Patients describe pain in a variety of ways, but often as burning or nogging [2]. FM affects about 1–5% of the world population. The incidence is higher in women than in men, and the median age range of manifestation is between 30 and 35 years [3]. Fibromyalgia has a strong genetic component, and studies suggest that the disorder has familial clustering and genetic predisposition [4]. Researchers have found associations between the development of FM and specific polymorphisms of genes involved in serotoninergic, dopaminergic, and catecholaminergic pathways. The etiopathogenesis of FM is thought to involve complex interactions between genetic predisposition and environmental and biological factors, with central sensitization playing an important role [1, 5]. FM shows a marked familial aggregation, indicating a genetic predisposition to this disorder. Although the exact etiology remains unknown, current evidence points to a significant genetic component in the development and severity of FM which can be associated with a spectrum of diseases, including infections, diabetes, rheumatic diseases, and psychiatric or neurological comorbidities [6]. Patients suffering from FM are characterized by significantly lower mental and physical health scores than the general population and other patients with chronic illnesses. The poor quality of life of patients with FM is reflected by the massive healthcare costs of patients, who frequently seek medical attention [1]. Some studies have shown that between 35 and 50% of patients with FM were not working [7]. The etiology of FM remains unknown, although it is supposed to be caused by a combination of genetic, environmental, and psychological factors including nutrition [8]. There are still no united, universally accepted treatment guidelines for FM, that is why treatment approaches are often symptomatic, including various types of diets [9]. Nutritional interventions used in FM management have been shown to be effective in reducing the symptoms. Clinical

trials with vitamin D, magnesium, iron, and probiotic supplementation have shown promising results in the chronic pain, anxiety, depression, cognitive function, sleep pattern, and gastrointestinal (GI) symptoms of FM. Also, weight loss seems to be associated with both a reduction of inflammation and improvement in the quality of life of patients with FM, thus suggesting that body weight control could have a role in providing treatment to these patients [10].

In the following review, we summarize available research for a correlation between FM and nutrition, and try to propose a new approach of neuronutrition management [11] in integrative programs of FM treatment.

MATERIALS AND METHODS

According to Paré and Kitsiou [12] and the PRISMA-S checklist [13], we conducted a comprehensive literature review using PubMed, Web of Science, and Medline. The chosen purpose of the study was to consider neuronutrition [13] as a new promising approach to FM treatment. We used the search terms: (fibromyalgia) AND (nutrition) OR (diet) OR (supplements). Other keywords used in this study are: "musculoskeletal pain", "chronic pain", and "nutritional interventions". We included the articles on clinical medical research. The exclusion criteria were articles of fundamental medicine and clinical trials performed before 2005. We concluded data from the suitable articles with available full texts and provided analyzed information with pictured schemes and resulting summaries. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

DIETARY APPROACH IN FM TREATMENT

FM was originally considered a non-inflammatory pain syndrome [14]. Symptoms of FM were previously attributed to dysfunction in central nociceptive sensory processing [15], which was explained by altered pain perception in FM patients, generalized hypersensitivity to unpleasant stimuli, altered cognitive functions, and sleep disturbances [16]. However, recent studies have shown that inflammatory changes can lead to central sensitization and chronic pain [17]. FM has an inflammatory component due to elevated levels of inflammatory cytokines such as IL-6 and decreased levels of anti-inflammatory cytokines like IL-10 [18]. Another study [19] reported increased serum levels of IL-1R antibody in FM patients and hypothesized the role of IL-6 toward the hypersensitivity to pain, fatigue, and depression. Since FM is a multifactorial disease, in which proinflammatory factors and central sensitization are currently considered to play a major role [14, 20], treatment should include pharmacological and non-pharmacological approaches. Among non-pharmaceutical strategies, there is growing evidence suggesting a potential beneficial effect of nutrition [21].

According to recent studies, vegetarian and vegan diets can be successfully used in FM management [22], as plant-based diets have a positive anti-inflammatory effect on gut microbiome and, in general, help resist systemic inflammation [23]. Meta-analysis provided evidence that vegan or vegetarian diets are associated with lower C reactive protein concentrations compared to an omnivorous diet in apparently healthy individuals and therefore may be a nutritional approach to reducing the risk of chronic disease [24]. Vegetarians consume large amounts of grains, fruits, vegetables, legumes, and nuts. Although the health benefits of these food components have been widely researched, there is no consensus on their anti-inflammatory effects. According to a meta-analysis [25], the anti-inflammatory effects of vegan and vegetarian diets depend on the type of food eaten, as different studies have shown conflicting results, presumably due to the different compositions of various plant-based foods. A vegetarian diet contains anti-inflammatory substances, such as phytosterols, spices, salicylic acid, and dietary fiber. Phytosterols in particular are considered

to be potent anti-inflammatory agents that can decrease inflammatory markers [26]. Donaldson et al. [22] investigated the effect of vegetarian diet in FM patients, emphasizing increased, compared to conventional diets, vitamin A intake in the form of carrot juice. The diet also contained fresh fruits, salads, raw vegetables, nuts, seeds, whole grain products, tubers, flaxseed oil, and extra virgin olive oil. Alcohol, caffeine, foods containing refined sugar, corn syrup, refined and/or hydrogenated oil, refined flour, dairy, eggs, and all meat were recommended to avoid. Self-reported questionnaires (FIQ, SF-36, QOL) were used to control the results. A vegetarian diet produced improvements in all FM symptoms for 19 of 30 participants. A systematic review [27] analyzed six studies, including four clinical trials and two cohort studies. The participants followed a vegetarian diet, with two clinical trials also including other physical therapies. The results showed significant improvements in quality of life, pain, sleep quality, anxiety, depression, and general health. Therefore, the review suggests that, to improve FM symptoms, physical exercise and an energy deficit are necessary, as elevated BMI levels have been directly linked to increased pain and functional status in FM patients [28].

According to a systematic review [29], half of FM patients have at least one functional gastrointestinal disorder (FGID), including irritable bowel syndrome (IBS). Both FM and functional gastrointestinal disorders (FGIDs) are thought to be linked to dysfunction of autonomic nervous system, which can lead to central sensitization, and may have a mutual reinforcing effect [30, 31]. The low-FODMAPs diet (LFD diet) has been successfully used to treat functional gastrointestinal disorders in various patient groups [32, 33]. To improve the quality of life of patients with FM and FGID, it is possible to use the LFD as an individual approach [34]. A low fermentable oligo-, di- and monosaccharides, alcohols and polyols diet is characterized by an exclusion of all dairy products, all cereals except rice, cashew, all fruit other than banana, citrus, pineapple, red berries, strawberries and kiwi, and all vegetables other than pumpkin, cabbage, lettuce, tomato, carrot and cucumber, for a 4-week period [34]. Marum et al. investigated the effect of LFD in FM patients. Assessment tools used were: Revised Fibromyalgia Impact Questionnaire, Fibromyalgia Survey Questionnaire, Severity Score System, Euro-QOL quality of life instrument, and Visual Analogue Scale (VAS). LFD therapy proved to have a highly positive effect on symptoms in FM patients and significantly improved the quality of life. In addition, the reduction in GI symptoms associated with the LFD was linked to a decrease in pain and functional impact [34], suggesting a possible connection between these symptoms and changes in the intestinal microbiota.

Another condition that may contribute to FGID in FM patients is non-celiac wheat sensitivity (NCWS) [35], a condition in which GI and extraintestinal symptoms are triggered by wheat in the absence of celiac disease (CD) or wheat allergy. Extraintestinal symptoms of NCWS are similar to those of FM [36], which is thought to have an immunological component. It has been suggested that both innate and adaptive immune responses play a role in NCWS [37], and may share some triggers with FM [35]. Based on this hypothesis, a gluten-free diet may be a non-pharmacological intervention for patients with FM and gluten sensitivity [36]. After 8 weeks on a gluten-free diet) [38], 30 of 63 patients experienced improved symptoms of FGID and FM, according to questionnaires. Additionally, an increase in the CD4+/CD8+ ratio among FM + NCWS patients after a gluten-free diet was observed, as well as a reduction in IL-17 and IL-22 levels. After the gluten-free diet, there was a statistically significant decrease in cytokine production [38].

NUTRITIONAL SUPPLEMENTS

In addition to a diet, personalized treatment for FM may also include the use of supplements.

Vitamin D

Observational studies have suggested a possible link between vitamin D deficiency and chronic pain, particularly in FM [39, 40]. Moreover,

vitamin D deficiency may have a role in central sensitization [41]. Several studies [42, 43] have confirmed the role of 25OHD deficiency in chronic musculoskeletal pain. Twenty-seven women and three men who fulfilled American College of Rheumatology criteria for FM, with serum calcifediol levels below 80 nmol/L (32 ng/mL) were included in a double-blind, placebo-controlled study. Depending on their serum calcifediol levels, the verum group received 2400 IU (serum calcifediol levels < 60 nmol/L) or 1200 IU (serum calcifediol levels 60–80 nmol/L) of cholecalciferol (vitamin D3) daily, dissolved in a triglyceride solution, with the aim of keeping calcifediol levels between 80 and 120 nmol/L. The placebo group received the triglyceride solution without cholecalciferol [44]. The study showed a remarkable and statistically significant reduction of mean scores on VAS in the treatment group [44].

Putative mechanisms by which vitamin D may be beneficial in FM include:

1. Modulation of nociceptive transmission in skeletal muscles, and its deficiency may lead to hyperinnervation and hypersensitivity to musculoskeletal pain. [45]
2. Vitamin D has anti-inflammatory and immunomodulatory effects. In particular, the vitamin can reduce the production of prostaglandin E2, which helps to regulate inflammatory pathways [40].
3. Vitamin D affects the synthesis and functioning of neurotransmitters, including serotonin, the level of which is altered in FM [46].

Magnesium

Magnesium can reduce inflammation and pain associated with FM symptoms. People with FM often have low magnesium levels, which reduces exercise capacity and increases inflammation in the body [47] and spasms. It plays a critical role in muscle relaxation and neurotransmitter functions. The underlying mechanism of magnesium's effects lies in its important role in preventing central sensitization, which is considered to be the primary mechanism underlying FM. Magnesium blocks *N*-methyl-D-aspartate (NMDA) receptors in a voltage-dependent manner, preventing the development of central sensitization. Magnesium deficiency has been associated with muscle pain, fatigue, difficulty sleeping, and anxiety—common symptoms of FM. This is thought to be due to magnesium's role in the regulation of muscle function and adenosine triphosphate (ATP) production. Magnesium is essential for ATP synthesis because ATP is stored in the body as a magnesium-ATP compound. Low ATP levels are common in people with FM, and this is thought to play a significant role in the development of many symptoms [48]. Magnesium is also involved in the regulation of hormone synthesis, including norepinephrine, which is often found to be overproduced in FM patients. This hormonal dysregulation is thought to contribute to the pathogenesis of FM [49]. In addition, magnesium is involved in the regulation of various nerve receptors, such as NMDA and 5-HT3, which are involved in the development of neuropathic pain experienced by FM patients. Magnesium's ability to block these receptors may help alleviate some types of FM pain [49].

Vitamin B12

Putative mechanisms of Vitamin B12's effect on the course of FM [46] include:

1. Inhibition of inflammatory mediators: vitamin B12 has been shown to inhibit inflammatory mediators known to contribute to pain.
2. Enhancing inhibitory signals in the pain pathway: vitamin B12 has been found to increase the effectiveness of norepinephrine and 5-hydroxytryptamine as inhibitory signals in the pain pathway, resulting in reduced pain perception.
3. Stimulating regeneration of damaged nerves and inhibiting spontaneous ectopic neuronal activity: it has been reported that vitamin B12 promotes regeneration of damaged nerves and inhibits spontaneous ectopic neuronal activity, which is associated with

gratuitous pain and increased sensitivity to pain.

Clinical studies have confirmed the potential benefit of vitamin B12 in the treatment of FM. One study showed that patients with FM who received frequent B12 injections with supplemental oral intake of B9 reported symptom relief, although the treatment was less effective in patients using opioids for pain management and more effective in patients taking thyroid hormones due to hypothyroidism [50]. In another study, daily administration of 1000 µg of oral vitamin B12 for 50 days was shown to significantly improve FM severity and anxiety scores in patients [51].

Coenzyme Q10

Coenzyme Q10 (CoQ10) plays a crucial role in the electron transport chain of mitochondria, contributing to the production of adenosine triphosphate (ATP), the main energy currency of cells. In FM, there is a decrease in mitochondrial mass and CoQ10 levels, leading to impaired energy production and increased oxidative stress [52]. This compound is a powerful anti-oxidant that helps to protect cells from oxidative damage caused by reactive oxygen species (ROS). In FM, excess ROS formation can contribute to pain and inflammation, so the anti-oxidant properties of CoQ10 help to reduce these symptoms. CoQ10 has been shown to regulate gene expression, particularly genes involved in the chronic inflammatory response, and has shown anti-inflammatory properties [53], suggesting that CoQ10 may help to mitigate the inflammatory component of FM [54]. Although research is still in its early stages, CoQ10 shows promise in reducing both pain and anxiety in people with FM [46].

Probiotics

Another class of promising supplements for FM treatment are probiotics. There is growing evidence linking diseases to the presence (or absence) of certain bacteria in the digestive system. Up to 60% of people with IBS have FM, and, conversely, up to 70% of people with FM experience symptoms of IBS [10, 46]. A number of studies have shown that people with IBS experience noticeable changes in their gut bacteria, which may contribute to its symptoms. Probiotics have shown promising results in improving symptoms of anxiety, IBS, and depression, which are common in FM [46]. Probiotics have shown promise in the treatment of FM by modulating the gut microbiota–brain axis.

Studies have shown that probiotics can improve attention, reduce errors in cognitive tasks, increase impulsivity, improve decision-making, and reduce depressive symptoms and anxiety in patients with FM [55]. These effects have been attributed to the regulation of the gut microbiota, which may influence pain, depression, sleep quality, and overall cognitive and emotional status in people with FM. Although more research is needed to fully understand the extent of probiotics' effects on cognitive function and emotional status in FM, current evidence suggests a promising role for probiotics as a therapeutic agent for the treatment of FM symptoms [56].

Lipids

The mechanism of action of omega-3 fatty acids in FM lies in their anti-inflammatory properties, which target the neuroinflammation that is a key factor in this disease. Omega-3 fatty acids, particularly EPA and DHA and their derivatives, such as resolvins, maresins, and protectins, can stimulate the cessation of inflammation by acting on immune cells. This action helps to break the cycle of neuroinflammation associated with FM [57]. In addition, a balance of saturated and unsaturated fats, including omega-3 and omega-6, may influence endocannabinoid production, contributing to FM pain relief (Fig. 1). Omega-3 fatty acids help to reduce pain intensity and fatigue and to improve sleep quality in patients with FM [58].

Studies on combination anti-pain therapy have been around for a long time. Thus, in 2015, Del Giorno et al. conducted prospective and retrospective observational studies on the

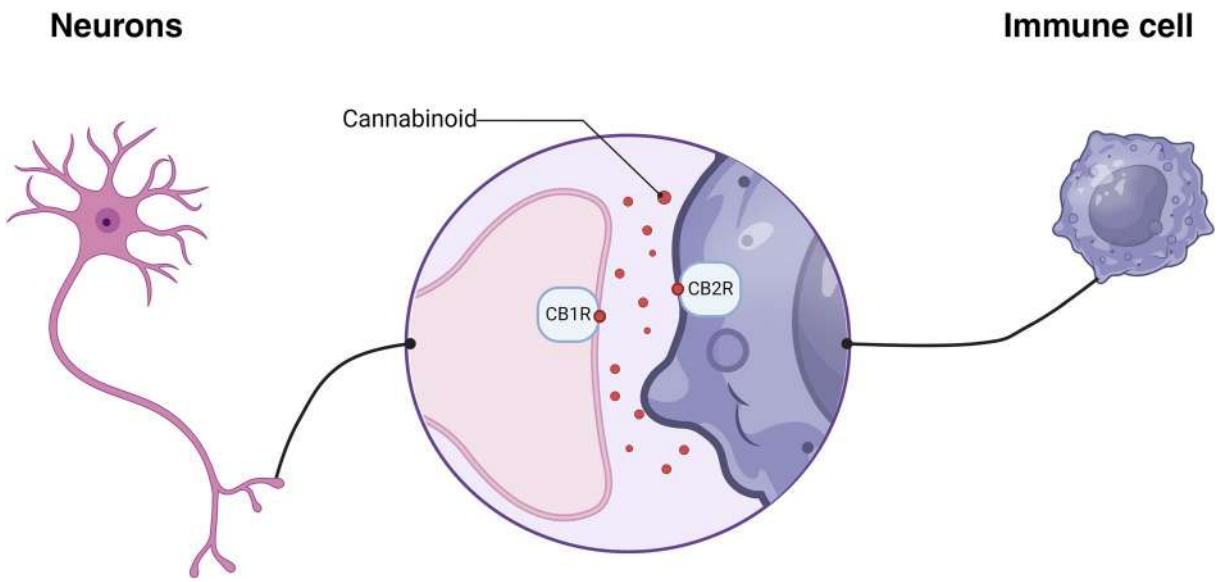

Fig. 1 Endocannabinoid system. *CB1R* cannabinoid receptor 1, *CB2R* cannabinoid receptor 2

efficacy of the combination of duloxetine (DLX) and pregabalin (PGB) for the treatment of FM syndrome, and the possibility of additional benefits with the addition of the lipid signaling molecule palmitoylethanolamide (PEA) [59]. The study showed that the combination of DLX + PGB reduced the number of pain points and pain intensity after 3 and 6 months of treatment. And when PEA was added to the DLX + PGB combination, there was further significant improvement in pain symptoms compared to DLX + PGB alone [60].

Melatonin

Melatonin has been used for a long time in neurology and in a number of pain syndromes, including headache and neurodegenerative and sleep disorders; FM is no exception [61]. The mechanism of action of melatonin in FM includes various pathways that contribute to its efficacy in the treatment of this disease. Melatonin, a potent endogenous antioxidant, plays a critical role in regulating physiological processes, such as circadian rhythms, pain modulation, mood, and immune balance (Fig. 2) [62]. In FM, melatonin has been shown to improve sleep quality, pain levels, and the pain threshold by enhancing the descending endogenous pain-modulating system [63]. This improvement is associated with decreased melatonin nuclear receptor expression and enhanced cytokine production in lymphocytic and monocytic cell lines, indicating its anti-inflammatory effects [64]. In addition, the analgesic effect of melatonin is mediated through activation of supraspinal sites, inhibition of spinal nociception, and modulation of various neurobiological systems, including GABAergic, opioid, and glutamatergic systems [65]. Overall, melatonin's ability to affect multiple pathways involved in the pathophysiology of FM makes it a promising adjunctive treatment for this chronic pain syndrome [66, 67].

S-adenosylmethionine (SAMe)

S-adenosylmethionine (SAMe) is a naturally occurring compound that plays a crucial role in various cellular processes, including methylation reactions, transsulfuration, and aminopropylation. In the context of FM, SAMe has been studied for its potential therapeutic benefits in alleviating symptoms.

SAMe's mechanism of action in FM includes:

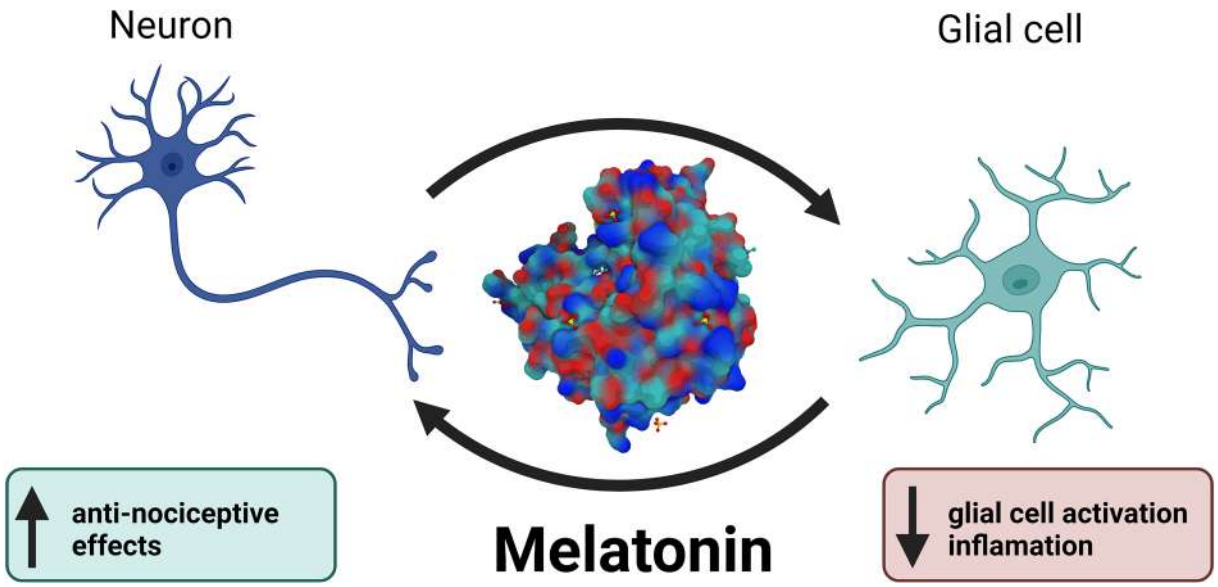

Fig. 2 The effect of melatonin in nociception

1. Methylation and gene expression: SAMe is a key player in the methylation process, which involves the transfer of a methyl group from SAMe to various molecules. This process is essential for the regulation of gene expression, particularly in the context of pain signaling pathways. In FM, altered methylation patterns have been observed, leading to changes in gene expression that contribute to the development and maintenance of chronic pain [68].
2. Pain modulation: SAMe has been shown to modulate pain transmission by influencing the activity of pain-related neurotransmitters, such as serotonin and dopamine. By increasing the levels of these neurotransmitters, SAMe can help reduce pain perception [69].
3. Inflammation reduction: SAMe has anti-inflammatory properties, which are thought to contribute to its therapeutic effects in FM. By reducing inflammation, SAMe may help alleviate symptoms such as pain, fatigue, and stiffness [70].
4. Neuroprotection: SAMe has been found to have neuroprotective properties, which may help protect against the neurodegenerative changes associated with FM. This neuroprotection can contribute to the overall therapeutic benefits of SAMe in FM treatment [70].
5. Synergistic effects: SAMe may also exhibit synergistic effects when combined with other treatments, such as painkillers or antidepressants, which can enhance its therapeutic potential in FM management [69, 70].

Acetyl-L-Carnitine

Acetyl-L-carnitine (ALA) has shown promise as a treatment for FM due to its potential mechanisms of action:

1. ALA modulates neurotransmitters such as acetylcholine, serotonin, and dopamine, which are involved in pain perception and mood regulation [71, 72]. This suggests that ALA may help alleviate cognitive and mood disorders often associated with FM.
2. ALA targets neurotrophic factors such as nerve growth factor and metabotropic glutamate receptors through epigenetic mechanisms [72].
3. ALA has anti-oxidant properties and protects against oxidative stress, which may be beneficial given the potential

role of mitochondrial dysfunction and neuroinflammation in the pathogenesis of FM [72, 73].

4. In a randomized controlled trial, ALA in combination with the antidepressant drug duloxetine, and the anticonvulsant drug pregabalin was shown to effectively treat the symptoms of FM [71, 73]. The combination therapy resulted in significant improvement in pain, fatigue, sleep, and depression compared to duloxetine and pregabalin alone.

Curcumin

Curcumin, the active compound in turmeric, has demonstrated potential benefit for the treatment of FM symptoms due to its anti-inflammatory and anti-oxidant properties [74–77]. Putative mechanisms of action include:

Decreased production of pro-inflammatory cytokines: curcumin can block the production of IL-12 by CD4, CD8, and NK cells, thereby reducing inflammation [77].

Enhancement of anti-oxidant capacity: curcumin increases the levels of anti-oxidant enzymes such as catalase, superoxide dismutase, and glutathione in the nervous system, skeletal muscles, and circulatory system, mitigating oxidative stress [74].

Modulation of neuroinflammation: curcumin may reduce the release of inflammatory mediators from spinal glia (microglia and astrocytes), reducing neuronal excitability and improving chronic pain [75].

We summarize all relevant data on potential nutrients and its mechanisms for FM management following neuronutritional approach in Fig. 3.

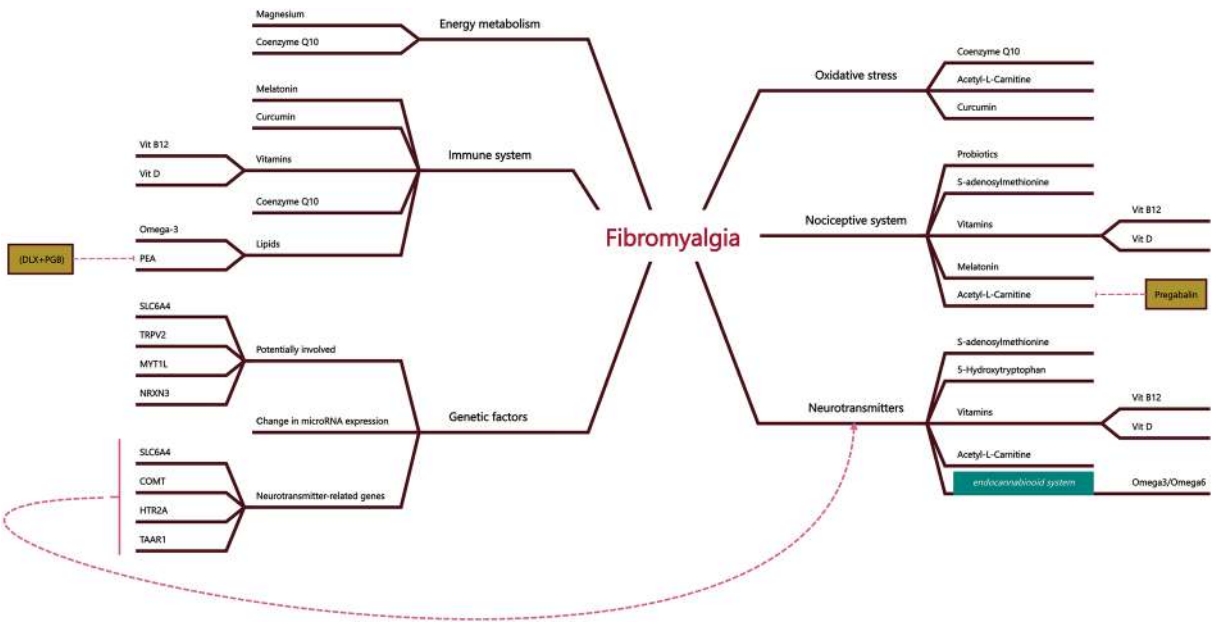

Fig. 3 Neuronutritional approach to FM management: nutrients and mechanisms. *PEA* palmitoylethanolamide, *DLX + PGB* combination of duloxetine and pregabalin, *SLC6A4* solute carrier family 6 member 4 gene, *TRPV2* transient receptor potential cation channel subfamily V member 2 gene, *MYT1L* myelin transcription factor 1 like gene, *NRXN3* neurexin 3 gene, *COMT* catechol-*O*-methyltransferase gene, *HTR2A* 5-hydroxytryptamine receptor 2A gene, *TAAR1* trace amine associated receptor 1 gene

THE SYNERGISTIC EFFECT OF PHYSICAL EXERCISE AND NUTRITIONAL INTERVENTIONS

The synergistic effect of exercise and nutrition in treating FM symptoms occurs when low-impact aerobic exercise is combined with a balanced diet. Regular aerobic exercise, such as walking, swimming, or cycling, has been shown to improve fitness, reduce pain and fatigue, and increase the ability to perform daily tasks in people with FM [78, 79]. Exercise is essential to maintain muscle strength and flexibility, control weight, and improve overall well-being in people with FM, which can also change the levels of endorphins and serotonin, which affect pain threshold, mood, and anxiety [78].

A synergistic effect is possible only with the synergistic work of medical specialists, occupational therapists, nutritionists, rehabilitation specialists, and other experts, taking into account the comorbidities of specific patients [79]. In addition, there is evidence in the literature, including meta-analyses, comparing the effectiveness of combinations of physical and dietary interventions. For example, a 2022 meta-analysis evaluated the effectiveness of acupuncture, intravenous lidocaine, and diet compared to other treatments, such as physiotherapy and placebo, in patients with FM. Acupuncture resulted in the greatest improvement in quality of life, pain, and depression levels compared to the group receiving placebo. Physiotherapy also showed significant improvement in quality of life. However, lidocaine and diet showed no significant differences compared to placebo [80].

CONCLUSION

FM is a complex syndrome characterized by chronic widespread pain, fatigue, sleep disturbances, and other functional symptoms. Current research suggests that both dietary interventions and nutritional supplements may play a role in treating FM symptoms. Neuronutrition interventions could help clinicians to provide personalized non-pharmocogical recommendations for patients with FM based on their symptoms and mechanisms of nutrient action. However, evidence is still emerging, and further well-designed randomized controlled trials are needed to develop the most effective and safe nutritional strategies for patients with FM. A personalized multidisciplinary approach combining diet, supplements, exercise, and other therapies appears to be the best strategy for managing FM.

ACKNOWLEDGEMENTS

We would like to express our gratitude to all the participants of this study for their invaluable contributions. Figs.1 and 2 were created with BioRender.com

Author Contributions. Anastasiia Badaeva conducted the primary research and drafted the initial manuscript Alexey Danilov, Anastasiia Kosareva, Mariia Lepshina, Yulia Vorobyeva, Viacheslav Novikov, Andrey Danilov contributed to the reviewing and critical revision of the manuscript. All authors reviewed and approved the final draft of the submitted manuscript.

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was waived for the authors.

Data Availability. Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Anastasiia Badaeva, Anastasiia Kosareva, Mariia Lepshina, Yulia Vorobyeva, Viacheslav Novikov declare that they have no conflicts of interest. Alexey Danilov and

Andrey Danilov are Editorial Board members of Pain and Therapy. Alexey Danilov and Andrey Danilov were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

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

REFERENCES

1. Sarzi-Puttini P, Giorgi V, Marotto D, Atzeni F. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. Nat Rev Rheumatol. 2020;16(11):645–60. https://doi.org/10.1038/s41584-020-00506-w. (**Epub 2020 Oct 6**).

2. Plazier M, Ost J, Stassijns G, De Ridder D, Vanneste S. Pain characteristics in fibromyalgia: understanding the multiple dimensions of pain. Clin Rheumatol. 2015;34(4):775–83. https://doi.org/10.1007/s10067-014-2736-6. (**Epub 2014 Jul 22**).

3. Siracusa R, Paola RD, Cuzzocrea S, Impellizzeri D. Fibromyalgia: pathogenesis, mechanisms, diagnosis and treatment options update. Int J Mol Sci. 2021;22(8):3891. https://doi.org/10.3390/ijms22083891.

4. Park DJ, Kang JH, Yim YR, Kim JE, Lee JW, Lee KE, Wen L, Kim TJ, Park YW, Lee SS. Exploring genetic susceptibility to fibromyalgia. Chonnam Med J. 2015;51(2):58–65. https://doi.org/10.4068/cmj.2015.51.2.58.

5. Al Sharie S, Varga SJ, Al-Husinat L, Sarzi-Puttini P, Araydah M, Bal'awi BR, Varrassi G. Unraveling the complex web of fibromyalgia: a narrative review. Medicina (Kaunas). 2024;60(2):272. https://doi.org/10.3390/medicina60020272.

6. Lichtenstein A, Tiosano S, Amital H. The complexities of fibromyalgia and its comorbidities. Curr Opin Rheumatol. 2018;30(1):94–100. https://doi.org/10.1097/BOR.0000000000000464.

7. Mukhida K, Carroll W, Arseneault R. Does work have to be so painful? A review of the literature examining the effects of fibromyalgia on the working experience from the patient perspective. Can J Pain. 2020;4(1):268–86. https://doi.org/10.1080/24740527.2020.1820858.

8. Low LA, Schweinhardt P. Early life adversity as a risk factor for fibromyalgia in later life. Pain Res Treat. 2012;2012: 140832. https://doi.org/10.1155/2012/140832.

9. Lowry E, Marley J, McVeigh JG, McSorley E, Allsopp P, Kerr D. Dietary interventions in the management of fibromyalgia: a systematic review and best-evidence synthesis. Nutrients. 2020;12(9):2664. https://doi.org/10.3390/nu12092664.

10. Pagliai G, Giangrandi I, Dinu M, Sofi F, Colombini B. Nutritional interventions in the management of fibromyalgia syndrome. Nutrients. 2020;12(9):2525. https://doi.org/10.3390/nu12092525.

11. Badaeva AV, Danilov AB, Clayton P, Moskalev AA, Karasev AV, Tarasevich AF, Vorobyeva YD, Novikov VN. Perspectives on neuronutrition in prevention and treatment of neurological disorders. Nutrients. 2023;15(11):2505. https://doi.org/10.3390/nu15112505.

12. Paré G, Kitsiou S. Chapter 9 methods for literature reviews. In: Lau F, Kuziemsky C, editors. Handbook of eHealth evaluation: an evidence-based approach. Victoria: University of Victoria; 2017. p. 27.

13. Rethlefsen ML, Kirtley S, Waffenschmidt S, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. Syst Rev. 2021;10:39. https://doi.org/10.1186/s13643-020-01542-z.

14. Desmeules JA, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum. 2003;48:1420–9.

15. Ceko M, Bushnell MC, Gracely RH. Neurobiology underlying fibromyalgia symptoms. Pain Res Treat. 2012. https://doi.org/10.1155/2012/585419.

16. Holton KF, Kindler LL, Jones KD. Potential dietary links to central sensitization in fibromyalgia: past reports and future directions. Rheum Dis Clin North Am. 2009;35:409–20.

17. Malhotra D, Saxena AK, Dar SA, Kumar V, Nasare N, Tripathi AK, Banerjee BD. Evaluation of cytokine levels in fibromyalgia syndrome patients and its relationship to the severity of chronic pain†. J Musculoskelet Pain. 2012;20(3):164–9. https://doi.org/10.3109/10582452.2012.704141.

18. 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 (Oxford). 2001;40(7):743–9. https://doi.org/10.1093/rheumatology/40.7.743.

19. Rodriguez-Pintó I, Agmon-Levin N, Howard A, Shoenfeld Y. Fibromyalgia and cytokines. Immunol Lett. 2014;161(2):200–3. https://doi.org/10.1016/j.imlet.2014.01.009. (**Epub 2014 Jan 23**).

20. Elma Ö, Yilmaz ST, Deliens T, Coppieters I, Clarys P, Nijs J, Malfliet A. Nutritional factors in chronic musculoskeletal pain: unravelling the underlying mechanisms. Br J Anaesth. 2020;125(2):e231–3. https://doi.org/10.1016/j.bja.2020.03.024. (**Epub 2020 Apr 28**).

21. Donaldson MS, Speight N, Loomis S. Fibromyalgia syndrome improved using a mostly raw vegetarian diet: an observational study. BMC Complement Altern Med. 2001;1:7. https://doi.org/10.1186/1472-6882-1-7. (**Epub 2001 Sep 26**).

22. Nijs J, Elma Ö, Yilmaz ST, Mullie P, Vanderweeën L, Clarys P, Malfliet A. Nutritional neurobiology and central nervous system sensitisation: missing link in a comprehensive treatment for chronic pain? Br J Anaesth. 2019. https://doi.org/10.1016/j.bja.2019.07.016.

23. Menzel J, Jabakhanji A, Biemann R, Mai K, Abraham K, Weikert C. Systematic review and meta-analysis of the associations of vegan and vegetarian diets with inflammatory biomarkers. Sci Reports. 2020. https://doi.org/10.1038/s41598-020-78426-8.

24. Haghighatdoost F, Bellissimo N, Totosy de Zepetnek JO, Rouhani MH. Association of vegetarian diet with inflammatory biomarkers: a systematic review and meta-analysis of observational studies. Public Health Nutr. 2017;20(15):2713–21. https://doi.org/10.1017/s1368980017001768.

25. Loizou S, Paraschos S, Mitakou S, et al. Chios mastic gum extract and isolated phytosterol tirucallol exhibit antiinflammatory activity in human aortic endothelial cells. Exp Biol Med (Maywood). 2009;234:553–61.

26. Nadal-Nicolás Y, Miralles-Amorós L, Martínez-Olcina M, Sánchez-Ortega M, Mora J, Martínez-Rodríguez A. Vegetarian and vegan diet in fibromyalgia: a systematic review. Int J Environ Res Public Health. 2021;18(9):4955. https://doi.org/10.3390/ijerph18094955.

27. Shapiro JR, Anderson DA, Danoff-Burg S. A pilot study of the effects of behavioral weight loss treatment on fibromyalgia symptoms. J Psychosom Res. 2005;59(5):275–82. https://doi.org/10.1016/j.jpsychores.2005.06.081.

28. Erdrich S, Hawrelak JA, Myers SP, Harnett JE. A systematic review of the association between fibromyalgia and functional gastrointestinal disorders. Therap Adv Gastroenterol. 2020;8(13):1756284820977402. https://doi.org/10.1177/1756284820977402.

29. Martínez-Martínez L-A, Mora T, Vargas A, et al. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. J Clin Rheumatol. 2014;20:146–50.

30. Palma-Ordóñez JF, Moreno-Fernández AM, Ramírez-Tejero JA, Durán-González E, Martínez-Lara A, Cotán D. Implication of intestinal microbiota in the etiopathogenesis of fibromyalgia: a systematic review. Int J Rheum Dis. 2024;27(1): e15021. https://doi.org/10.1111/1756-185X.15021.

31. Black CJ, Staudacher HM, Ford AC. Efficacy of a low FODMAP diet in irritable bowel syndrome: systematic review and network meta-analysis. Gut. 2022;71(6):1117–26. https://doi.org/10.1136/gutjnl-2021-325214. (**Epub 2021 Aug 10**).

32. van Lanen AS, de Bree A, Greyling A. Efficacy of a low-FODMAP diet in adult irritable bowel syndrome: a systematic review and meta-analysis. Eur J Nutr. 2021;60(6):3505–22. https://doi.org/10.1007/s00394-020-02473-0. (**Erratum in: Eur J Nutr. 2021 Jun 28**).

33. Silva AR, Bernardo A, Costa J, Cardoso A, Santos P, de Mesquita MF, Vaz Patto J, Moreira P, Silva ML, Padrão P. Dietary interventions in fibromyalgia: a

systematic review. Ann Med. 2019;51(sup1):2–14. https://doi.org/10.1080/07853890.2018.1564360.

34. Marum AP, Moreira C, Tomas-Carus P, et al. A low fermentable oligo-di-mono-saccharides and polyols (FODMAP) diet is a balanced therapy for fibromyalgia with nutritional and symptomatic benefits. Nutr Hosp. 2017;34:667–74.

35. Isasi C, Colmenero I, Casco F, et al. Fibromyalgia and non-celiac gluten sensitivity: a description with remission of fibromyalgia. Rheumatol Int. 2014;34:1607–12.

36. Losurdo G, Principi M, Iannone A, et al. Extra-intestinal manifestations of non-celiac gluten sensitivity: an expanding paradigm. World J Gastroenterol. 2018;24:1521–30.

37. Di Liberto D, Mansueto P, D'Alcamo A, et al. Predominance of type 1 innate lymphoid cells in the rectal mucosa of patients with non-celiac wheat sensitivity: reversal after a wheat-free diet. Clin Transl Gastroenterol. 2016;7: e178.

38. Schinocca C, Di Liberto D, Mansueto P, Pizzo ML, Grasso G, Messana E, Dieli F, Ciccia F, Guggino G, Carroccio A. Effect of the gluten-free diet on quality of life, gastrointestinal symptoms and immune system in patients with fibromyalgia and non-celiac wheat sensitivity. Fibromyalgia and non-celiac wheat sensitivity. J Biotechnol Biomed. 2021;4:211–27.

39. 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;5(2):28. https://doi.org/10.1186/s41927-018-0035-6.

40. Liu X, Nelson A, Wang X, Farid M, Gunji Y, Ikari J, et al. Vitamin D modulates prostaglandin E2 synthesis and degradation in human lung fibroblasts. Am J Respir Cell Mol Biol. 2014;50(1):40–50.

41. Habib AM, Nagi K, Thillaiappan NB, Sukumaran V, Akhtar S. Vitamin D and its potential interplay with pain signaling pathways. Front Immunol. 2020;11:820.

42. Schreuder F, Bernsen RM, van der Wouden JC. Vitamin D supplementation for nonspecific musculoskeletal pain in nonWestern immigrants: a randomized controlled trial. Ann Fam Med. 2012;10:547–55.

43. Gendelman O, Itzhaki D, Makarov S, Bennun M, Amital H. A randomized double-blind placebo-controlled study adding high dose vitamin D to analgesic regimens in patients with musculoskeletal pain. Lupus. 2015;24:483–9.

44. Wepner F, Scheuer R, Schuetz-Wieser B, Machacek P, Pieler-Bruha E, Cross HS, Hahne J, Friedrich M. Effects of vitamin D on patients with fibromyalgia syndrome: a randomized placebo-controlled trial. Pain. 2014;155(2):261–8. https://doi.org/10.1016/j.pain.2013.10.002.

45. Sarzi-Puttini P, Giorgi V, Atzeni F, Roberto G, Kosek E, Choy E, Bazzichi L, Häuser W, Ablin J, Aloush V, Buskila D, Amital H, Da Silva J, Perrot S, Morlion B, Polati E, Schweiger V, Coaccioli S, Varrassi G, Batticciotto A. Diagnostic and therapeutic care pathway for fibromyalgia. Clin Exp Rheumatol. 2021;39 Suppl 130:120–7. https://doi.org/10.55563/clinexprheumatol/zcp5hz.

46. Haddad HW, Mallepalli NR, Scheinuk JE, Bhargava P, Cornett EM, Urits I, Kaye AD. The role of nutrient supplementation in the management of chronic pain in fibromyalgia: a narrative review. Pain Ther. 2021;10(2):827–48. https://doi.org/10.1007/s40122-021-00266-9.

47. Kim YS, Kim KM, Lee DJ, Kim BT, Park SB, Cho DY, Suh CH, Kim HA, Park RW, Joo NS. Women with fibromyalgia have lower levels of calcium, magnesium, iron and manganese in hair mineral analysis. J Korean Med Sci. 2011;26(10):1253–7. https://doi.org/10.3346/jkms.2011.26.10.1253. (**Epub 2011 Oct 1**).

48. Boulis M, Boulis M, Clauw D. Magnesium and fibromyalgia: a literature review. J Prim Care Community Health. 2021;12:21501327211038430. https://doi.org/10.1177/21501327211038433.

49. Macian N, Dualé C, Voute M, Leray V, Courrent M, Bodé P, Giron F, Sonneville S, Bernard L, Joanny F, Menard K, Ducheix G, Pereira B, Pickering G. Short-term magnesium therapy alleviates moderate stress in patients with fibromyalgia: a randomized double-blind clinical trial. Nutrients. 2022;14(10):2088. https://doi.org/10.3390/nu14102088.

50. Regland B, Forsmark S, Halaouate L, Matousek M, Peilot B, Zachrisson O, Gottfries CG. Response to vitamin B12 and folic acid in myalgic encephalomyelitis and fibromyalgia. PLoS One. 2015;10(4): e0124648. https://doi.org/10.1371/journal.pone.0124648.

51. Gharibpoor F, Ghavidel-Parsa B, Sattari N, Bidari A, Nejatifar F, Montazeri A. Effect of vitamin B12 on the symptom severity and psychological profile of fibromyalgia patients; a prospective pre-post study. BMC Rheumatol. 2022;6(1):51. https://doi.org/10.1186/s41927-022-00282-y.

52. Pallotti F, Bergamini C, Lamperti C, Fato R. The roles of coenzyme Q in disease: direct and indirect involvement in cellular functions. Int J Mol Sci.

2021;23(1):128. https://doi.org/10.3390/ijms23010128.

53. Pastor-Maldonado CJ, Suárez-Rivero JM, Povea-Cabello S, Álvarez-Córdoba M, Villalón-García I, Munuera-Cabeza M, Suárez-Carrillo A, Talaverón-Rey M, Sánchez-Alcázar JA. Coenzyme Q10: novel formulations and medical trends. Int J Mol Sci. 2020;21(22):8432. https://doi.org/10.3390/ijms21228432.

54. Mantle D, Hargreaves IP, Domingo JC, Castro-Marrero J. Mitochondrial dysfunction and coenzyme Q10 supplementation in post-viral fatigue syndrome: an overview. Int J Mol Sci. 2024;25(1):574. https://doi.org/10.3390/ijms25010574.

55. Varrassi G, Cereda E, Ruoppolo G, Mercieri M, Muscaritoli M. The drug called food and its role as a therapy for chronic patients: a comprehensive narrative review. 1. 2024;https://doi.org/10.4081/ahr.2024.6.

56. Roman P, Estévez AF, Miras A, Sánchez-Labraca N, Cañadas F, Vivas AB, Cardona D. A pilot randomized controlled trial to explore cognitive and emotional effects of probiotics in fibromyalgia. Sci Rep. 2018;8(1):10965. https://doi.org/10.1038/s41598-018-29388-5.

57. Herbst EA, Paglialunga S, Gerling C, Whitfield J, Mukai K, Chabowski A, Heigenhauser GJ, Spriet LL, Holloway GP. Omega-3 supplementation alters mitochondrial membrane composition and respiration kinetics in human skeletal muscle. J Physiol. 2014;592(6):1341–52. https://doi.org/10.1113/jphysiol.2013.267336.

58. Bourke SL, Schlag AK, O'Sullivan SE, Nutt DJ, Finn DP. Cannabinoids and the endocannabinoid system in fibromyalgia: a review of preclinical and clinical research. Pharmacol Ther. 2022;240:108216. https://doi.org/10.1016/j.pharmthera.2022.108216.

59. Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in Fibromyalgia: results from prospective and retrospective observational studies. Pain Ther. 2015. https://doi.org/10.1007/s40122-015-0038-6.

60. Paladini A, Fusco M, Cenacchi T, Schievano C, Piroli A, Varrassi G. Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: a pooled data meta-analysis. Pain Physician. 2016;19(2):11–24.

61. Danilov AB, Danilov AB, Kurushina OV, Shestel EA, Zhivolupov SA, Latysheva NV. Safety and efficacy of melatonin in chronic tension-type headache: a post-marketing real-world surveillance program. Pain Ther. 2020;9(2):741–50. https://doi.org/10.1007/s40122-020-00207-y.

62. Sarzi-Puttini P, Giorgi V, Atzeni F, Roberto G, Kosek E, Choy E, Bazzichi L, Hauser W, Ablin J, Aloush V, Buskila D, Amital H, Da Silva J, Perrot S, Morlion B, Polati E, Schweiger V, Coaccioli S, Varrassi G, Batticciotto A. Fibromyalgia position paper. Clin Exp Rheumatol. 2021. https://doi.org/10.55563/clinexprheumatol/i19pig.

63. Schweiger V, Secchettin E, Perini G, Martini A, Donadello K, Gottin L, Balzo G, Varrassi G, Polati E. Quality of life and psychological assessment in patients with Fibromyalgia Syndrome during COVID-19 pandemic in Italy: prospective observational study. Signa Vitae. 2022;18:41–6. https://doi.org/10.22514/sv.2021.127.

64. González-Flores D, López-Pingarrón L, Castaño MY, Gómez MÁ, Rodríguez AB, García JJ, Garrido M. Melatonin as a coadjuvant in the treatment of patients with fibromyalgia. Biomedicines. 2023;11(7):1964. https://doi.org/10.3390/biomedicines11071964.

65. de Zanette SA, Vercelino R, Laste G, Rozisky JR, Schwertner A, Machado CB, Xavier F, de Souza IC, Deitos A, Torres IL, Caumo W. 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. https://doi.org/10.1186/2050-6511-15-40.

66. Danilov A, Kurganova J. Melatonin in chronic pain syndromes. Pain Ther. 2016;5(1):1–17. https://doi.org/10.1007/s40122-016-0049-y.

67. Kurganova YM, Danilov AB. The role of melatonin in the treatment of chronic back pain. Neurosci Behav Physi. 2016;46:737–42. https://doi.org/10.1007/s11055-016-0303-0.

68. Gerra MC, Carnevali D, Ossola P, González-Villar A, Pedersen IS, Triñanes Y, Donnini C, Manfredini M, Arendt-Nielsen L, Carrillo-de-la-Peña MT. DNA methylation changes in fibromyalgia suggest the role of the immune-inflammatory response and central sensitization. J Clin Med. 2021;10(21):4992. https://doi.org/10.3390/jcm10214992.

69. Arnold LM, Clauw DJ. Challenges of implementing fibromyalgia treatment guidelines in current clinical practice. Postgrad Med. 2017;129(7):709–14. https://doi.org/10.1080/00325481.2017.1336417.

70. Pfalzer AC, Choi SW, Tammen SA, Park LK, Bottiglieri T, Parnell LD, Lamon-Fava S.

S-adenosylmethionine mediates inhibition of inflammatory response and changes in DNA methylation in human macrophages. Physiol Genomics. 2014;46(17):617–23. https://doi.org/10.1152/physiolgenomics.00056.2014. (**Epub 2014 Jul 15**).

71. Saracoglu I, Akin E, Aydin Dincer GB. Efficacy of adding pain neuroscience education to a multimodal treatment in fibromyalgia: a systematic review and meta-analysis. Int J Rheum Dis. 2022;25(4):394–404. https://doi.org/10.1111/1756-185X.14293.

72. Rossini M, Di Munno O, Valentini G, Bianchi G, Biasi G, Cacace E, Malesci D, La Montagna G, Viapiana O, Adami S. Double-blind, multicenter trial comparing acetyl-L-carnitine with placebo in the treatment of fibromyalgia patients. Clin Exp Rheumatol. 2007;25(2):182–8.

73. Sarzi-Puttini P, Giorgi V, Di Lascio S, Fornasari D. Acetyl-L-carnitine in chronic pain: a narrative review. Pharmacol Res. 2021;173: 105874. https://doi.org/10.1016/j.phrs.2021.105874.

74. Chiechio S, Copani A, Gereau RW 4th, Nicoletti F. Acetyl-L-carnitine in neuropathic pain: experimental data. CNS Drugs. 2007;21(Suppl 1):31–46. https://doi.org/10.2165/00023210-200721001-00005.

75. Shen CL, Schuck A, Tompkins C, Dunn DM, Neugebauer V. Bioactive compounds for fibromyalgia-like symptoms: a narrative review and future perspectives. Int J Environ Res Public Health. 2022;19(7):4148. https://doi.org/10.3390/ijerph19074148.

76. Hasriadi, Dasuni WasanaVajragupta PWO, Rojsitthisak P, Towiwat P. Mechanistic insight into the effects of curcumin on neuroinflammation-driven chronic pain. Pharmaceuticals (Basel, Switzerland). 2021;14(8):777. https://doi.org/10.3390/ph14080777.

77. Abdelrahman KM, Hackshaw KV. Nutritional supplements for the treatment of neuropathic pain. Biomedicines. 2021;9(6):674. https://doi.org/10.3390/biomedicines9060674.

78. Fernández-Araque A, Verde Z, Torres-Ortega C, Sainz-Gil M, Velasco-Gonzalez V, González-Bernal JJ, Mielgo-Ayuso J. Effects of antioxidants on pain perception in patients with fibromyalgia—a systematic review. J Clin Med. 2022;11(9):2462. https://doi.org/10.3390/jcm11092462.

79. Carrasco-Querol N, González Serra G, Bueno Hernández N, Gonçalves AQ, Pastor Cazalla M, Bestratén Del Pino P, Montesó Curto P, Caballol Angelats R, Fusté Anguera I, Sancho Sol MC, Castro Blanco E, Vila-Martí A, Medina-Perucha L, Fernández-Sáez J, Dalmau Llorca MR, Aguilar MC. Effectiveness and health benefits of a nutritional, chronobiological and physical exercise primary care intervention in fibromyalgia and chronic fatigue syndrome: SYNCHRONIZE + mixed-methods study protocol. Medicine (Baltimore). 2023;102(17): e33637. https://doi.org/10.1097/MD.0000000000033637.

80. Bjørklund G, Dadar M, Chirumbolo S, Aaseth J. Fibromyalgia and nutrition: therapeutic possibilities? Biomed Pharmacother. 2018;103:531–8. https://doi.org/10.1016/j.biopha.2018.04.056. (**ISSN 0753-3322**).

81. Almutairi NM, Hilal FM, Bashawyah A, Dammas FA, Yamak Altinpulluk E, Hou J-D, Lin J-A, Varrassi G, Chang K-V, Allam AE-S. Efficacy of acupuncture, intravenous lidocaine, and diet in the management of patients with fibromyalgia: a systematic review and network meta-analysis. Healthcare. 2022;10:1176. https://doi.org/10.3390/healthcare1007117.