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Review

Fibromyalgia and ozone treatment. A comprehensive clinical narrative review

Fibromialgia y tratamiento con ozono. Una revisión narrativa clínica exhaustiva

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Keywords

Ozone therapy
Ozone treatment
Fibromyalgia
MAHT
O3SS
MiAHT.

Abstract

Fibromyalgia (FM) is a chronic, multi factorial disorder, predominantly affecting women, characterized by widespread chronic musculoskeletal pain, sleep disturbances, fatigue and psychological symptoms, all of which significantly impair quality of life. Actually, current standard therapeutic strategies remains only partially effective. Ozone therapy (OT), particularly when administered via autohemotherapy (MAHT), has been proposed as a potential complementary treatment targeting underlying mechanisms such as: oxidative stress and inflammation via an induce repeted controlled oxidative stress and the activation of endogenous antioxidant and immunomodulatory pathways. This clinical narrative review evaluates studies published between 2022 and 2026 on the complementary use of ozone therapy in FM.

Fibromyalgia syndrome (FMS) is a disorder with no cure, characterized by exclusionary criteria from diagnosis, as well as chronic widespread muscle pain, debilitating fatigue, and reduced quality of life. Even though there are numerous pharmacological and non-pharmacological treatment options available to treat FMS, many patients fail to respond to conventional therapies and are therefore classified as being refractory to treatment. In this scenario, complementary modalities such as using ozone as a treatment modality have become a viable therapeutic options, however, Further researches are needed especially, randomized control trials (RCTs) to support and confirm these clinical data to confirm their efficacy. The clinical improvements noted to date with OT are most likely attributable to its antioxidant, anti-inflammatory, and immunomodulatory effects targeting the three central mechanisms of FM (e.g. oxidative stress, central sensitization and immune dysregulation). The recurrent of symptoms in some patients suggest that ongoing clinical benefit may entail optimizing or repeating the ozone treatment protocol. While there is some encouraging evidence, variability among study methodology and design limit the generalization of these results. Additional randomized controlled trials with larger sample sizes that are well-designed are needed to validate these evidences, determine the optimal treatment regimens and define the long-term safety of ozone therapy for FM.

The purpose of this narrative comprehensive review is t1o provide further information of the latest evidences in favor of OT for FM and discuss some aspect of therm.

Palabras clave

Ozonoterapia
Tratamiento con ozono
Fibromialgia
Autohemoterapia Mayor (AHTM)
Estrés Oxidativo y Nitrosativo (O&NS)
Autohemoterapia Menor (AHTm)

Resumen

La fibromialgia (FM) es un trastorno crónico y multifactorial que afecta predominantemente a mujeres. Se caracteriza por dolor musculoesquelético generalizado, alteraciones del sueño, fatiga y síntomas psicológicos, que en conjunto producen un importante deterioro de la calidad de vida. En la actualidad, las estrategias terapéuticas convencionales ofrecen una eficacia limitada y con frecuencia solo consiguen un alivio parcial de los síntomas.

La ozonoterapia (OT), especialmente cuando se administra mediante autohemoterapia mayor (AHTM), ha sido propuesta como un tratamiento complementario potencial dirigido a mecanismos fisiopatológicos subyacentes, tales como el estrés oxidativo y la inflamación, a través de la inducción repetida de un estrés oxidativo controlado y la activación de vías antioxidantes e inmunomoduladoras endógenas.

Esta revisión narrativa clínica evalúa los estudios publicados entre 2022 y 2026 sobre el uso complementario de la ozonoterapia en pacientes con fibromialgia.

El síndrome de fibromialgia (SFM) es una enfermedad sin cura conocida, cuyo diagnóstico se basa fundamentalmente en criterios clínicos y de exclusión. Se caracteriza por dolor muscular crónico generalizado, fatiga incapacitante y una disminución significativa de la calidad de vida. Aunque existen numerosas opciones terapéuticas farmacológicas y no farmacológicas, muchos pacientes no responden adecuadamente a los tratamientos convencionales y son considerados refractarios al tratamiento.

En este contexto, modalidades terapéuticas complementarias como la ozonoterapia han emergido como una alternativa potencialmente útil. No obstante, se requieren más investigaciones, especialmente ensayos clínicos aleatorizados y controlados (ECA), que permitan confirmar y respaldar los resultados clínicos observados hasta el momento.

Las mejorías clínicas descritas con la ozonoterapia parecen estar relacionadas principalmente con sus efectos antioxidantes, antiinflamatorios e inmunomoduladores, actuando sobre tres de los mecanismos fisiopatológicos centrales de la fibromialgia: el estrés oxidativo, la sensibilización central y la disfunción inmunológica.

La recurrencia de los síntomas observada en algunos pacientes sugiere que el mantenimiento de los beneficios clínicos podría requerir la optimización o repetición periódica de los protocolos de tratamiento con ozono.

Aunque la evidencia disponible resulta prometedora, la heterogeneidad metodológica y las diferencias en el diseño de los estudios limitan la generalización de los resultados. Por ello, son necesarios ensayos clínicos aleatorizados, controlados y bien diseñados, con muestras de mayor tamaño, para validar estas evidencias, determinar los regímenes terapéuticos óptimos y establecer la seguridad a largo plazo de la ozonoterapia en la fibromialgia.

El objetivo de esta revisión narrativa integral es proporcionar una actualización de las evidencias más recientes favorables al uso de la ozonoterapia en la fibromialgia, así como analizar y discutir sus principales implicaciones clínicas.

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INTRODUCCIÓN

Fibromyalgia Syndrome (FMS) is a complex chronic illness that presents with widespread musculoskeletal pain, specific regions of tenderness, fatigue, sleep disturbances, problems processing information (cognitive dysfunction), and hypersensitivity (central sensitization). It has been shown that a combination of environmental factors, neurophysiological factors, genetic predisposition can lead to an increase in the likelihood of developing FMS (PEERJ, 2025). Additionally, in today's healthcare system, a major problem of public concern with respect to FM is the large financial impact of FM on total healthcare spending. One study performed using a large database of patients in the U.S. found that the average total cost to provide 12 months of care for patients with FMS was approximately three times greater than the costs associated with providing care for patients without FMS (Lloyd et al., 2012). On the other hand, due to the ease of use, low cost, and few side effects of ozone therapy, this treatment is becoming increasingly popular (Hidalgo-Tallón et al., 2022). Moreover, FMS's patients having chronic musculoskeletal pain and fatigue, have a reduced compliance to common treatment and frequently a poor response as well (Bazzicchi L. 2024).

These FM patients that usually are poor responder to treatment have also a high tendency to respond to the placebo effect, leading them to seek complementary or alternative therapies, most of the time. The evidence-based medicine (EBM) does not have enough pharmaceutical options available to help treat the wide complex variety of symptoms associated with FM; therefore, non-pharmaceutical therapies, including ozone therapy (OT), could prove and have proven to be beneficial. Several studies have demonstrated that OT can be effective in reducing pain, treating sleep disorders and improving fatigue in individuals with FMS. (Bazzicchi L. 2024). FMS treatment is typically categorized into pharmacological and non-pharmacological approaches. Pharmacological treatments include for example tricyclic antidepressants (e.g., amitriptyline, nortriptyline), serotonin–nor-epinephrine re-uptake inhibitors (e.g., duloxetine), anticonvulsants (e.g., pregabalin), and in selected cases, weak opioids such as tramadol. Non-pharmacological strategies encompass cognitive-behavioral therapy, mindfulness-based interventions, and structured physical exercise programs (including aerobic training, tai chi, yoga, and qigong), as well as alternative approaches such as acupuncture and hypnosis (Filipovic et al., 2025 PEERJ). OT has gained recognition and popularity because it is relatively simple to perform, low cost and because it is thought to be very safe. Preliminary clinical study results also demonstrated that patients with FMS experienced short-term or longer-term improvement in their level of pain, fatigue, and difficulty sleeping after treatment with ozone therapy. It is theorized that these benefits may have resulted from ozone's antioxidant, anti-inflammatory, or immunomodulatory effects. However, due to different kinds of research methods that have been used in studies, small numbers of subjects included in trials, and no good quality randomized controlled trials of OT, definitive conclusions cannot yet be made about using ozone therapy for the treatment of FMS (Hidalgo-Tallón et al., 2022; Üşen et al., 2025 PEERJ). OT can be given through different ways: all of these routes will depend upon where the therapy is needed, and what medical condition is being treated. In addition to administering ozone therapy intravenously (O3SS), ozone can be administered subcutaneously, intradiscally, intra-articular or intramuscular for local therapy effect. Other methods of administration such as urethral, vaginal and rectal insufflation (RI), as well as autohemotherapy (AHT), have been described in the literature, and utilized with excellent outcomes. Their clinical efficacy and safety have not been adequately established yet and will require additional validation from well-designed research studies to ensure that the safety profile is complete (Bocci 2006 PEERJ).

Brief history: For many centuries FM has been documented as a clinical condition; however, FM's evolution over the years has led to many variations of its definition. Early descriptions of chronic musculoskeletal pain can be found back to Hippocrates, while many believe similar symptoms are even described in the biblical book of Job. Historically, the understanding and terminology of FM have undergone numerous changes. For instance, the word fibrositis, which originated from both the French and the English medical communities in the mid-

19th century, was created as a means for documenting a chronic pain disorder involving connective or fibrous tissue. In 1976, however, the American Rheumatism Association officially sanctioned the term" fibromyalgia "as a syndrome (but not a separate disease entity) according to Hench in 1977.[Capra F. Book. *Oxygen and Ozone therapy. The use of ozone therapy in fibromyalgia: mechanisms and scientific evidence*]

FM is currently characterized by chronic widespread musculoskeletal pain persisting for more than three months, affecting muscles, tendons, ligaments, and other soft tissues. This pain is often associated with specific tender points. There are many additional systemic features commonly experienced by patients diagnosed with fibromyalgia that include asthenia (affecting approximately 90% of patients), neuropsychiatric disorders (i.e., anxiety, depression, panic disorder and/or alexithymia) and significant sleep problems. The most common sleep disturbance experienced by individuals with FM is reduced deep sleep, with frequent nocturnal awakenings. Furthermore between the different symptoms experienced by FM's patients we have: cognitive dysfunction (difficulties focusing, concentrating and remembering, commonly referred as "fibro fog"), wide-ranging neurological and somatic symptoms (muscle pain), as well as autonomic problems (migraines or headaches) are among the many symptoms someone with FM could experience. Other examples of symptoms include: photophobia, numbness, facial pain, extreme sensitivity to touch, tingling, back pain and muscle stiffness, spasms of the esophagus and legs, fasciculations, restless legs syndrome, joint pain, anterior chest pain, gastro-intestinal symptoms (nausea, spastic abdominal pain, irritable bowel syndrome) (R.M. Mallaeva 2018), general vascular symptoms (postural orthostatic tachycardia syndrome, orthostatic hypotension), sleep apnea, Raynaud's syndrome, primary dysmenorrhea, multiple chemical other sensitivities, and interstitial cystitis. Because of the great diversity in symptoms experienced by individuals with FM and the lack of biological and/or radiological tests that confirm FM, that can significantly delay a clinical diagnosis from occurring up to two years from the time that an individual first experiences signs and symptoms of FM (Edgar H A 2016).

Prevalence: Per the new diagnostic criteria from the American College of Rheumatology, FM has a worldwide prevalence rate of 2.7%; 4.2% females diagnosed and 1.4% of males diagnosed with FM. Prevalence increases with age, peaking between 60 and 79 years. Gender: Females are twice as likely to be diagnosed as males, with female prevalence rates estimated between 2.4% and 6.8%. Among patients in tertiary care pain management clinics, over 40% may meet the criteria for FM . Plus there is a regional variation: studies show a 0.7% to 11.4% prevalence in urban areas versus 0.1% to 5.2% in rural areas. [Egil A Forse 2024].

Introduction to FM/FMS, a complex field? FM is a complex central nervous system (CNS) syndrome characterized mostly by hyperalgesia and allodynia and peripheral pain. The nature of the pain is defined as nociplastic according to the latest international classification and is characterized by altered nervous sensitization both centrally and peripherally. [Paroli M. 2024]. The pain associated with FM is caused by a disruption in the balance between the excitatory and inhibitory roles of several different neurotransmitters that are required for the process of nociception. These neurotransmitters include, but are not limited to, serotonin and norepinephrine, both of which are considered to be inhibitory, and substance P, glutamate, and amino acids, all of which are considered to be excitatory. The amplification of the pain signal is a result of the hypoactivity of the inhibitory neurotransmitters and hyperactivity of the excitatory neurotransmitters. As such, the physiologic basis for the wide distribution of pain in FM can be explained. Many of the neurotransmitters involved in the amplification of the pain signal also play a role in many of the other functions of the CNS and autonomic nervous system, which is why so many other symptoms of FM, including insomnia and depression, can be attributed to abnormal

physiologic processes. [Macfarlane GJ, et al. 2017]. FMS appears to have a combination of central and peripheral causes as well. Recent studies indicate that skin and muscles peripheral receptors have an altered in function: increased sensitivity of vanilloid receptors (TRPV), acid-sensing ion channels (ASICs), and purinergic receptors. The alterations in the peripheral modulations of nociception appear to be responsible for the heightened sensitivity to pain in FMS. The relationship between the central and peripheral mechanisms of fibromyalgia is quite complex. Peripheral nociceptive input may trigger central sensitization and maintaing the central sensitization. The CNS also is believed to play a central role in modulating the central neurons' perception of pain. This amplification of pain is thought to be a central mechanism involved in FM pain. This amplification adds to the development of neurogenic inflammation that leads to many of the distinctive characteristics of fibromyalgia such as: widespread tenderness and pain, swelling of the periphery, and cognitive dysfunction . [Dominguez MG. 2025]

Diagnosis of FM: FM is characterized by clinical heterogeneity and there are currently no definitively accepted biomarkers for diagnostic purposes. FM was officially recognized as an accepted clinical disorder in October 1990, following the first diagnostic criteria established by the American College of Rheumatology (ACR) related to tender points, throug physical examination, which involved 11/18 predetermined and standard sites where pressure dramatically increased the patient's experience of pain for at least 3 months. Exclusion of other diagnoses that might account for the widespread pain present in FM must have been done. In 2010, updated criteria were defined based on the severity of the quality of pain distribution as well as the presence of additional symptoms (fatigue and depression; sleep disturbances, cognitive dysfunction) this more accurately demonstrated that FMS was a multi-dimensional disorder. Then, in 2016, additional changes were proposed in order to further refine the accuracy of diagnosis; however, these newer criteria for diagnosing FM have not yet gained widespread acceptance among clinicians around the world. [Sarzi-Puttini P. 2020]. Nonetheless, the complexity of diagnosis continues to challenge clinicians attempting to diagnose FM. Inherent to this challenge are the vast similarities (in terms of clinical presentation) that FM has with existing medical conditions, multiple phenotypically based FM presentations, and the high frequency of medical and psychiatric comorbidities that are seen among individuals with FM, and as such, incomplete assessments of FM-related symptoms occur as a result of these difficulties, thereby making it difficult for clinicians to accurately classify individuals with FM according to the ACR diagnostic criteria. In summary, establishing a universal and reliable diagnostic criterion for diagnosing FM continues to be a significant barrier for clincians and researchers. [Bradford T. et al. 2023.]

Another curious example, which is not the topic of my discussion now, is about a recent study that has shown that individuals following a Mediterranean diet, specifically one, rich in the amino acid Tryptophan and the mineral Magnesium, had a large amount of anxiety, eating, mood and body image disorders reduced compared to fibromyalgic people not on this type of diet. Therefore, it is plausible that dietary patterns in by people who consume a large amount of pro-inflammatory foods may promote neuroinflammation processes and worsen clinical symptoms of those diagnosed FM. Also, there is an increasing amount of evidence that indicates a close association between FM and autoimmune or inflammatory disease, suggesting that FM often presents as a comorbidity in people who have conditions of immunological origins. [Martinez-Rodriguez A. et al. 2020].

OZONE GAS THERAPY AND ITS PROPOSED MECHANISM OF ACTION IN FM:

Based on the way ozone therapy could treat FM, it is thought that ozone therapy may work by regulating oxidative stress, reducing inflammation and maintaining cellular homeostasis. The exact mechanisms of action are still not well defined in the clinical environment, and; therefore, there is limited clinical and preclinical evidence to support their use.

Modulation of Oxidative Stress via Adaptive Responses

Fibromyalgia has been associated with an imbalance of reactive oxygen species (ROS) and antioxidant system with a state of increased oxidative stress as cause of FM. Ozone therapy when given in low doses, follow a phenomenon known as 'hormesis', which is a controlled ozone concentration that has been proposed as a way to create a mild and temporary form of oxidative stimulus. This controlled oxidative stress might activate the body's own antioxidant systems, leading to the upregulation of the activity of enzymes like: superoxide dismutase, catalase and glutathione peroxidase. However, the degree of clinically significant outcome due to this mechanism in FM is still not well defined. [Oktay Faysal 2025. PEERJ].

Activation of the Nrf2 Pathway

The main idea of OT is based on the stimulation of the Nfr2 (nuclear factor erythroid 2-related factor 2) pathway. This pathway is responsible for cellular defense against oxidative and inflammatory stress. Once activated, Nrf2 will migrate to the nucleus of the cell where it promotes the expression of numerous cytoprotective genes involved with antioxidant defense, detoxification, and cellular repair. Activation of the Nrf2 pathway may produce a number of downstream effects, including: [Franzini M. 2023.]

- Reduction of Neuroinflammation: Activation of the Nrf2 pathway has been linked to the downregulation of inflammatory mediators, such as TNF-alpha and IL-1beta. These mediators have been implicated in central sensitization and chronic pain.
- Cellular Protection and Repair: Activated Nrf2 may provide increased resistance to oxidative cell damage in both neuronal cells and non-neuronal cells as well as may provide additional support for the structural integrity of these cells. However, claims related to specific cellular repair mechanisms (i.e. myelin restoration) are speculative at this time and have not been adequately demonstrated in fibromyalgia.

- Mitochondrial Function Improvement: Nrf2 activation may modulate the balance between oxidative stress in the mitochondria and preserve the overall cellular energy metabolism. This may be important due to the documented association between mitochondrial dysfunction and fatigue, found in many individuals sick with FM, however, there is little direct clinical evidence to support this claim at this time. [Inguscio CR et al. 2026.]

Increased Blood Circulation & Metabolic Activity

Ozone enhances circulation, which subsequently allows for increased oxygen delivery by erythrocytes (red blood cells) to areas within the body where they are needed most (i.e. muscles, brain). These results are an increase in the amount of energy produced, less sensation of fatigue, and an improvement in cognitive function.
However, the extent to which these molecular effects translate into clinically meaningful outcomes remains still uncertain. The current evidence base is largely derived from experimental studies and small, methodologically heterogeneous clinical investigations, limiting causal inference. Accordingly, while OT represents a biologically plausible complementary strategy, its function and therapeutic validity in FM requires confirmation in rigorously designed, adequately powered randomized controlled trials. [Wanzhou Wang et al. 2022]

Further recent researches provide strong evidence that the role of inflammation is a central pivot in FM and show that inflammation can no longer be viewed as the result of FM; rather, it is one of the major

mechanisms by which FM develops and persists [Bains A. 2023]. Additional studies have demonstrated that patients with fibromyalgia have higher levels of systemic inflammatory markers when measured using the ELISA method than healthy controls. For example, C-Reactive Protein (CRP) is widely used to identify patients with low levels of systemic inflammatory disease [Beiner E at al. 2023-Zetterman T et al. 2022-Groven N. et al. 2019]. However, patients with fibromyalgia may have different CRP levels and not all FM patients have elevated CRP levels. Some research has indicated that this variability in CRP levels in FM patients may be due to other factors such as co-morbidities (e.g., obesity, diabetes, Hypertension, neurological diseases etc...) and coexisting inflammatory diseases [Meresh E at al. 2024]. Thus, the inflammatory state within the FM patient population may lead to a "catalytic response" that promotes an exacerbation of FM symptoms, especially the pain, which is at the core of this complex pathology. Considering this complex interaction between inflammation and FM, further investigations are necessary to allow new treatment and healthcare strategies for this condition.

The important role of inflammation in FM. The presence of elevated pro-inflammatory cytokines and diminished anti-inflammatory cytokines such as IL-4 and IL-13, as well as an increase in the number of activated mast cells within the FM patient population were evidenced through plasma protein analysis conducted with the ELISA assay. In addition, blood analyses of FM patients show a higher neutrophil/lymphocyte ratio and variations in the subsets of T lymphocytes (i.e. CD4+ T cells and NKT cells) when compared to health controls [Dominguez M.G. 2025]. The biomarkers in this study contribute to our understanding of the inflammatory processes associated with FM and may help facilitate future diagnostic tests. Furthermore, new research has revealed an intricate relationship between gut microbiome and FM; this will be explored in upcoming studies using fecal microbiota transplants (FMTs) from FM patients into germ-free mice to determine if the transplanted material will produce pain hypersensitivity in the recipient. Preliminary analysis indicates that FMTs from FM patients produce a pain hypersensitivity in the germ free recipients while healthy controls do not. These results suggest that the gut dysbiosis is present in the FM composite population [Cai W. et al. 2023-Fang H. et al. 2024]. This research establishes the validity of the 'gut dysbiosis in FM'. Inflammation is a key factor of this syndrome's (FM) development and maintenance. Inflammatory cytokines as well as peripheral (outside the central nervous system) immune activation can cause the activation of the nervous system resulting in activating a pain response and continuing to activate that response via vicious circle mechanisms. This creates a self-perpetuating feed-back loop whereby pain = inflammation = immune system activation = pain (and so on). [Dominguez MG. 2025.]

LITERATURE REVIEW: MAIN CLINICAL STUDIES OF OXYGEN-OZONE THERAPY IN FM BETWEEN 2022-2026

The treatment of fibromyalgia with oxygen-ozone was initiated in Germany (Berlin and Munich) in 1993.

Ozone therapy is no longer an experimental approach, but a therapy supported by a growing number of clinical trials that attest to its efficacy and safety.

In order to update the Review of Bazzichi L., 2024 here I summarize the following studies since 2022 up to now.

1. 2022 Tirelli U. et al. A study conducted in Italy, following the previous one dated 2019. This is a large number (n=200) study of FM patients diagnosed FM following the ACR redefined criteria 2010. These FM patients received 3-4 cycles of MAHT. The study showed that there were significant presence and magnitude of clinically relevant improvements in pain and functional capabilities during a short-term follow-up period (1 month). Specifically, approximately 76% of patients presented at

the 1 month follow-up with significantly increased functional muscular performance and decreased arthralgia. Further, 64.5% of patients reported clinically relevant decreases in the intensity of pain, based on the Pain Intensity Numeric Rating Scale (PI-NRS). Additionally, of the total patients, 23.5% experienced substantial clinical improvements with only two treatment sessions; however, 17.5% did not experience any improvements. Thus, there were also individual differences in the response to the treatment. The results of this data are consistent with previous completion of data on OT for the treatment of FM-related pain, fatigue, and quality of life.

2. 2022 Indra C. et al.: Clinical trial with a 69-year-old female diagnosed with FM, in Mexico. She was treated with a O_3SS treatment. At the beginning of the study, she completed a Visual Analog Scale (VAS) assessment to evaluate her pain as well as she underwent an evaluation for disturbances in sleep and psychological issues (i.e., anxiety and depression). She was also assessed for inflammation/ immunological biomarkers (CRP, rheumatoid factor (RF), ESR, monocytes, anti-streptolysin antibody, anti-CCP antibody level and Vit-D3 level). The patient's inflammatory markers (anti-streptolysin and anti-CCP) were elevated (RF 40 IU/mL, CRP 10.9 mg/L and monocyte 11.1%) , ESR was higher than normal (11 mm/h). Autoimmune-measured antibodies (anti-streptolysin. <200 IU/mL and anti-CCP <8) fell within the normal and/or undetermined range and her Vit-D3 was also in normal range (63.2pg/ mL). She received a total of 12 intravenous infusions of 250 mL O_3SS (0.9% NaCl); two times a week. Each infusion was delivered using continuous micro-bubbling to maintain a stable concentration of gas in the solution. The patient was treated via an initial dose of 5 µg/kg session for the first six infusions and thereafter the last six infusions she received a lower dose of 3 µg(kg)/infusion. At the end of the first six treatments, there was a sharp decrease in inflammatory markers. RF dropped by 50% (from 40 IU/mL to 20 IU/mL) while CRP decreased 79% (from 10.9 mg/L to 2.2 mg/L) over the same period. Monocytes decreased approximately 26% (from 11.1% to 8.2%), indicating an accompanying change in immune activation. From a clinical standpoint, the patient experienced a rapid and significant decrease in pain, decreasing from a VAS score of 9 at rest and 10 during exertion, to 1 at rest and 4 during physical activity within just 3-4 treatment sessions. There were also many positive changes in the psychological and functional areas after six weeks of therapy, including decreases in anxiety (10 -> 1), insomnia (10 -> 3), and depression (10 5).

3. 2023 Sucuoğlu: A randomized double blind placebo controlled study. A significant purpose of this research is to evaluate the effectiveness of ozone therapy (OT) as an alternative therapy along with the treatment of FMS. Twenty-six patients with FMS were randomly assigned to either OT (n=26) or placebo control (PC) (n=28) groups after completing the informed consent process. All subjects received OT via MAHT and MiAHT for two sessions weekly, for a total of ten sessions. The FIQ, PSQI, and 12-item Short-Form Health Survey (SF-12) questionnaires were administered both pre and post-treatment to quantify subjects' FMS symptoms and general health. In the comparison of both groups, at post-treatment there was a statistically significant improvement in the FIQ subscales (feel good and fatigue) and total PSQI score and the subscales of the PSQI (subjective sleep quality, sleep latency, and sleep disturbances)($p<0.05$) for the OT group compared to the PC group. In both groups, there was an improvement in the total FIQ score, however, the difference between groups was not statistically significant ($p>0.05$). The use of OT in conjunction with the method of AHT demonstrated an improvement in the subscale scores (feel good and fatigue) of FMS during the treatment phase and an improvement in overall sleep quality. However, changes in the post-treatment FIQ total score were not different in the ozone therapy group from the placebo control group.

4. 2025 Oktay: A retrospective study including 72 patients (68 females, 4 males) with FMS, the effects of a standardized MAHT protocol (10 sessions over 5 months period with progressively increasing ozone concentrations) were evaluated across multiple clinical domains. They received 2 sessions per week. The 1 st session with a dose of 100 ml patient's blood at [10 µg/ml] of O3 concentration and further the ozone concentration was gradually augmented at 30 µg/ml with a maximum cumulative

dose of 3000 µg of Ozone. Significant improvements were observed following treatment. Pain intensity, measured by the VAS, decreased from 7.76 ± 2.01 to 4.77 ± 2.20. Functional status, assessed by the FIQ, improved from 69.08 ± 16.01 to 56.18 ± 22.46. Sleep quality, evaluated using the PSQI, showed modest improvement (10.27 ± 3.37 to 9.61 ± 2.81), while quality of life, assessed via the Short Form-36 (SF-36), improved significantly across domains. All changes were statistically significant ($p < 0.001$). These findings suggest that MAHT may provide clinically relevant benefits in reducing pain and improving functional outcomes and quality of life in patients with FM. However, the retrospective design, absence of a control group, and short follow-up period limit the strength of causal inference. Given the known variability and placebo responsiveness of FMS, these results should be interpreted with caution. In conclusion, while MAHT appears to be a promising adjunctive intervention for fibromyalgia, further validation through large-scale, randomized controlled trials is required to establish its efficacy, safety, and long-term clinical relevance.

5. 2025 Kuculmez: A longitudinal cross-sectional study conducted at Baskent University Alanya Hospital on adults (aged 20-65yrs) diagnosed with FM following the American College of Rheumatology (ACR) (2010) criteria. Every patient received a course of treatment consisting of ten MAHT sessions over 2-3 weeks. 10 sessions of 100 ml of the subject's own blood with and 100 ml of O3 gas infused at 25 µg/ml. 20 females patients were treated with ozone MAHT at a concentration of 25 µg/ml, 2-3 times /week. 3 months of follow-up. Data for the sample size consisted of the demographic information as well as a thorough three-month-follow up questionnaire answered by each of the patients. Clinical assessments were made to evaluate pain levels using the Visual Analog Scale (VAS) and to evaluate functional ability.

This study compared FIQ score changes from baseline at 3 months after treatment. Patients displayed a median (min-max) VAS score of 9 (5-10) at the time of initial assessment, 3 (0-8) after completion of treatment, and 3 (1-8) in the first month, and 4 (1-8) in the third month. The FIQ median score of the patients had a baseline level of 73.29 (29.20 - 87.20), and post-treatment of 31.67 (7.01 - 66.99), 1 month of 24.8 (10.70 - 63.30), and 3 months of 24.67 (10.67 - 66.99). Statistically significant decreases in pain and functional improvements were measured in patients receiving OT ($p < 0.001$). Pain scores were reduced from baseline as a result of completing the treatment protocol using MAHT. Patients also reported improvement in their functional ability. Both of these results suggest MAHT may provide a positive benefit on FM's most common symptoms. Statistically significant decreases in pain and functional improvements were measured in patients receiving OT ($p < 0.001$).

6. 2025 Usen et al. A retrospective study evaluated the short- and medium-term efficacy of OT administered via MAHT in 25 patients with FMS (20 females and 5 males). Patients underwent to 10 treatment sessions of MAHT, with outcomes assessed at baseline, post-treatment, and at six-month follow-up using validated instruments (VAS, FIQ, HADS, PSQI, and FSS). 2 times per week. Key outcomes were measured using the VAS, FIQ, HADS (Hospital Anxiety and Depression Scale), PSQI and FSS. Follow-up of 6 months. 100 ml of blood patients was collected, 100 ml of Ozone gas was used at a concentration ranged between 10 µg/ml and 30 µg/ml.

Significant improvements were observed across all clinical domains immediately after treatment, including reductions in pain (VAS: 6.4 to 3.68, $p < 0.001$), functional impairment (FIQ: 59.2 to 39.08, $p < 0.001$), and tender point counts. Improvements in anxiety, depression, sleep quality, and fatigue were also reported. At six months, partial symptom recurrence was noted; however, most parameters remained improved compared to baseline. These findings suggest that ozone therapy may provide short- to medium-term symptomatic benefits in FMS.

7. 2026 Genovese A. et al. A Clinical Observational Report. MAHT treatment protocol involving 10 initial treatments with progressively more concentrated doses of ozone (30 µg/Nml – first 5 sessions to 50

µg/NmL – second 5 sessions) followed by maintenance therapy (once/month for 12 months) was used to treat 37 patients (32 women, 5 men) diagnosed with FM. They evaluated pain and sleep quality. 10 sessions of MAHT were performed. The pain was evaluated with Numerical Rating Scale (EVA, NRS) and sleep quality with PSQI. Clinical endpoints for evaluation were the NRS for pain and the PSQI for sleep quality. Clinical evaluations were completed throughout treatment, post-treatment and at the end of the follow-up period. Patients who had previously experienced pain showed significant decreases in pain intensity and improvements in sleep quality. Ozone MAHT provided patients with consistent symptom relief throughout the study. This study showed the efficacy of the ozone in reducing pain with furthermore a progressive sustained stability on pain (analgesic effect) over 12 months. The efficacy of treatment was seen from the 5th session onward. The average PSQI improved by 30% compared to baseline after 10 sessions, and it remains stable during the monthly follow-up as well. This study confirm the effectiveness of ozone AHT for the treatment of FM.

8. 2026 Ciftci et al. A Retrospective Clinical Study included 45 patients, diagnosed FM who had failed to respond to conventional treatments and underwent MAHT within the previous 6 months. 10 sessions of MAHT, 2 times a week. The objectives: evaluate the impact of MAHT as a treatment modality; to document clinical outcomes at baseline and three months post-treatment and to determine patient attitudes toward complementary medicine. Low doses at the beginning, 15 µg/ml up to 25 µg/ml. 100 ml of patient's blood with 100 ml of ozone gas was mixed. Clinical outcomes were assessed at baseline and three months following treatment. Measurements: pain intensity was measured using the VAS scale, functional status with the FIQ, and quality of life with the SF-12 scale. Holistic Complementary and Alternative Medicine Questionnaire (HCAMQ) was administered to assess patient attitudes toward complementary and alternative medicine. Statistical analyses were performed to compare baseline (J0) and post-treatment (3 months later) outcomes and to assess correlations between variables. Significant improvements were observed in all measured outcomes. Median VAS scores decreased from 8 to 4 ($p < 0.001$). Mean FIQ scores improved from 65.72 ± 10.50 to 40.91 ± 18.02 ($p < 0.001$; 95% CI 19.9–29.8). Both physical and mental component scores of the SF-12 increased significantly ($p < 0.001$). A strong positive correlation was identified between reductions in pain and improvements in functional status ($r = 0.817$, $p < 0.001$). Additionally, higher HCAMQ scores were negatively associated with clinical improvement. This study confirm the efficacy of ozone treatment in reduction of pain activities of daily life and quality of life in FM patients.

Table 1: Main studies and findings about ozone therapy in FM (2022 - 2026):

First author	Year	N° patients	Type of TT	[O2/O3]	N°of TT	Results
Tirelli (23)	2022	200	MAHT	200 ml pt's blood +200 ml O3, [45 µg/ml] 3-4 sessions.	3-4 cycles. sessions	Improvement in fatigue and mood.
Shen (26)	2022	123.De los cuales: 53MAHT y 50 controls	MAHT	100 ml pt´s blood + 100 ml O3, (20-40 µg/ml)	3 weeks.	Improvement in pain and mood.
Indra 2022	2022	1	O3SS	250ml O3SS, first 6 sessions at 5 µg/ml, second 6 sessions at 3 µg/ml,	12 sessions. Daily	Improvement in pain, sleep, mood and blood values (CRP, monocytes).
Sucuoglu (27)	2023	54. 26 TT, 28	MAHT/MiAHT	100 ml pt's blood + 100 ml O3, [ND]	2x/week 10 sessions	Improvement in FIQ subscale score (feeling good, fatigue).
Oktaj	2025	72	MAHT		10 sessions	Improvement sleep, and pain. QoL
Kuculmez	2025	20 females	MAHT	100 ml pt's blood, 100 ml O3 at 10-30 µg/ml	10 sessions. 2 x week.	Improvement in fatigue, better mood, sleep, anxiety and pain.
Usen	2025	25	MAHT	100 ml pt's blood, 100 ml O3 at 10-30 µg/ml	10 sessions. 2 x week.	Improvemet in FIQ subscale. Fatigue, better mood, sleep anxiety and pain.
Genovese	2026	37	MAHT	first 5 sessions, [30-50 µg/ml]. Second 5 sessions, 50 µg/Nml	One session x week. 10 sessions. 1x/month – 1 year.	Improvement in pain and sleep.
Ciftci	2026	45	MAHT	100 ml pt's blood, 100 ml O3 at 10-25 µg/ml	2 sessions x week. 10 sessions.	Improvement in pain and QoL

CONCLUSION

Fibromyalgia (FM) is a chronic and multifactorial disorder characterized by persistent widespread musculoskeletal pain, functional impairment, and a marked reduction in quality of life. Despite the availability of pharmacological and non-pharmacological interventions, a substantial proportion of patients continue to experience inadequate symptom relief, underscoring the need for complementary therapeutic strategies. In this context, ozone therapy (OT) has emerged as a potential complementary approach; however, its clinical relevance in FM remains to be clearly established through a comprehensive synthesis of the available evidence.

This clinical narrative review examined studies published between 2022 and 2026 investigating the complementary use of OT in FM. A wide spectrum of study designs was included, encompassing

case reports, retrospective analyses, observational studies, short- and medium-term clinical trials, longitudinal cross-sectional studies, and randomized double-blind placebo-controlled trials. The primary objective was to evaluate the consistency and robustness of therapeutic outcomes associated with OT across diverse clinical settings and methodological frameworks in respect of FMS through different clinical settings and methodologies between years 2022 and nowday.

Across the included literature, OT, particularly O3SS and MAHT, demonstrated consistent beneficial effects on key clinical outcomes. These included significant reductions in pain intensity, improvements in functional capacity, and enhancements in overall quality of life. Evidence from case reports provided detailed insights into individual-level responses, highlighting improvements not only in pain but also in sleep disturbances and inflammatory markers. These findings were corroborated by larger prospective and controlled studies, which reported statistically significant improvements across similar domains. Follow-up data further suggested that these benefits may be sustained over short- to medium-term periods.

The therapeutic effects observed are biologically plausible and likely attributable to the antioxidant, anti-inflammatory, and immunomodulatory properties of ozone. These mechanisms may directly target central components of FM pathophysiology, including oxidative stress, central sensitization, and immune dysregulation. Nevertheless, the recurrence of symptoms in a subset of patients indicates that sustained clinical benefit may depend on the optimization and potential repetition of treatment protocols.

OT may be of benefit to FM patients due to its potential role as an adjunctive treatment by modulating the biological processes underlying FM given FM has a multi-factorial psychophysiology including oxidative stress, central sensitization and immune dysregulation. Thus, OT may reduce FM symptoms and improve function by modulating the underlying biological processes. The biological basis for ozone therapy supports its use as a complementary treatment for patients with persistent symptoms while undergoing traditional multimodal/multidisciplinary treatment approaches. The overall evidence indicates that OT may provide a useful supplementary treatment modality for FM.

Despite these promising findings, the current evidence base is limited by substantial methodological heterogeneity. Variability in study design, sample size, treatment protocols, and the frequent absence of rigorous controls or double-blind procedures constrain the interpretability and generalizability of results. While retrospective and observational data consistently suggest reductions in pain and improvements in quality of life following OT, these findings must be interpreted with caution given the inherent limitations of such designs.

In summary, ozone therapy appears to represent a promising complementary modality in the management of FM, low cost and poor of sides effects, particularly for patients with persistent symptoms despite standard multidisciplinary care. However, definitive conclusions regarding its long-term efficacy, safety, and optimal clinical application cannot yet be established. Future research should prioritize large-scale, methodologically robust randomized controlled trials to standardize treatment protocols, clarify mechanisms of action, and determine the durability of therapeutic effects.

Abbreviations:

ACR: American College of Rheumatology
ADL: activities of daily living
CRP: C-Reactive Protein
EBM: evidence-based medicine

FIQ: Fibromyalgia Impact Questionnaire
FM: fibromyalgia
FMTs: microbiota transplants
FMS: fibromyalgia syndrome
FSS : fatigue severity scale
HADS Hospital Anxiety and Depression Scale
HCAMQ: Holistic Complementary and Alternative Medicine Questionnaire
IR: Intra Rectal
MAHT: Major Auto Hemo Therapy
MiAHT: Minor Auto Hemo therapy
Nfr2 (nuclear factor erythroid 2-related factor 2)
O3SS: Ozonated Saline Solution
OT: ozone therapy
PC: placebo control
PI-NRS: Pain Intensity Numeric Rating Scale
PSQI: Pittsburgh Sleep Quality Index
QoL: Quality of life
RCTs: randomized control trials
ROS: reactive oxygen species
SF-12: 12-item Short-Form Health Survey Questionnaire
VAS: Visual Analogic Scale

Main methods of ozone treatment used in patients with FM
Intra Rectal: IR
Major Auto Hemo Therapy: MAHT
Minor Auto Hemo Therapy: MiAHT
Ozonatez Saline Solution: SSO3

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