Review

Oxygen/ozone gas treatment of fibromyalgia syndrome: a narrative review

L. Bazzichi[1], V. Giorgi[2], G. Pellegrino[1], M. Di Franco[3], C. Iannuccelli[3], S. Bongiovanni[4], F. Galli[5], E. Piacentino[6], P. Sarzi-Puttini[1,4]

[1]*Rheumatology Unit, IRCCS Ospedale Galeazzi Sant'Ambrogio, Milan, Italy;*
[2]*Unità di Ricerca Clinica, Gruppo Ospedaliero Moncucco, Lugano, Switzerland;*
[3]*Division of Rheumatology, Department of Clinical Internal, Anaesthesiologic and Cardiovascular Sciences, Sapienza University of Rome, Italy;*
[4]*Department of Biomedical and Clinical Sciences, University of Milan, Italy;*
[5]*Department of Dynamic and Clinical Psychology, and Health Studies, Sapienza University of Rome, Italy;*
[6]*Pain Unit, IRCCS Ospedale Galeazzi Sant'Ambrogio, Milan, Italy.*

Laura Bazzichi, MD
Valeria Giorgi, MD
Greta Pellegrino, MD
Manuela Di Franco, MD
Cristina Iannuccelli, MD, PhD
Sara Bongiovanni, PhD
Federica Galli, PhD
Edoardo Piacentino, MD
Piercarlo Sarzi-Puttini, MD

Please address correspondence to:
Piercarlo Sarzi-Puttini
Rheumatology Unit,
IRCCS Ospedale Galeazzi Sant'Ambrogio,
Via Cristina Belgioioso,
20157 Milano, Italy.
E-mail: piercarlo.sarziputtini@gmail.com

Received on May 23, 2024; accepted in revised form on May yy, 2024.

J Environ Rheumatol 2024; 1: 15-19.

Key words: fibromyalgia, chronic pain, ozone therapy, oxygen/ozone therapy, treatment

Competing interests: none declared

ABSTRACT

Widespread musculoskeletal pain and fatigue can significantly reduce treatment compliance in patients with fibromyalgia (FM). These patients also frequently show a poor treatment response and are highly subject to placebo effects that induce approximately 60% to turn to complementary or alternative therapies. Given the limited pharmaceutical options for managing the variety of FM symptoms, non-pharmaceutical interventions such as oxygen/ozone gas therapy (ozone therapy) may be beneficial as some studies have shown that it is effective in treating pain, sleep disorders and fatigue in patients with chronic fatigue syndrome or FM. This review analyses seven studies that investigated the use of various forms of ozone administration, including major and minor autohemotherapy, and the rectal insufflation of ozone concentrations of 20-60 µg/mL, and found a consistent pattern of symptom improvement (reduced pain, improved sleep, and enhanced mental clarity) among FM patients. However, these studies were also characterised by potential limitations such as their small sample sizes, different treatment protocols, the absence of double-blinding techniques, and a lack of long-term follow-up data, thus suggesting a need for confirmatory controlled clinical trials. Nevertheless, despite these limitations, it seems that ozone therapy is a promising means of treating FM that merits further investigation in longer-term, large-scale and standardised trials.

Introduction

Fibromyalgia (FM) is characterised by chronic widespread pain, fatigue, sleep disturbances and functional symptoms, but the continuing debate concerning its aetiopathogenesis and diagnostic and classification criteria still raises doubts about its effective treatment (1) FM is the third most frequently encountered musculoskeletal condition: its prevalence increases with age, and FM patients often poorly respond to treatment and are highly subject to placebo effects (2). Although the development of more accurate diagnostic criteria has improved the rate of diagnosis, it is still under-recognised by a considerable proportion of physicians (3) because its pathogenesis is characterised by a unique multifactorial combination of genetic predisposition, personal experiences, emotional-cognitive factors, mind-body relationships, and variations in the patient's biopsychological ability to cope with stress (4). The multiple components of its pathogenesis and maintenance requires a multi-modal treatment approach that needs to be individually tailored as it is becoming increasingly widely recognised that the patients fall into various subgroups with different clinical characteristics (5). Consequently, although an evidence-based approach to FM management is always desirable, treatment is inevitably empirical and requires the creation of a strong alliance between physicians and patients in order to formulate shared and realistic therapeutic goals.

The many factors contributing to the development of FM mean that the condition represents mind-body hyperconnection rather than disconnection, and its treatment needs to be holistic, comprehensive, and characterised by integrated multidisciplinary interventions (6, 7). As it is a chronic pain syndrome that is believed to be influenced

by neuro-inflammation, its treatment can be divided into the four pillars of patient education, fitness, pharmacological treatment, and psychotherapy. We suggest a treatment strategy that not only takes into account the latest EULAR recommendations for the management of FM (5), but also reflects real-life clinical experience and realistic patient expectations and goals. Pharmacological treatment should be started immediately (mainly because patients are usually diagnosed years after symptom onset) (4), but it should also be complemented by one or more of the wide ranges of alternative interventions. Regarding this, Perrot *et al*. with their meta-analysis in 2014 suggested that the magnitude of the multidimensional effect of such an approach can exceed that of pharmacological treatment alone (8). Although the benefit of these interventions is still a subject of controversy (probably because the study designs are often weak and the quality of evidence is usually low), many of these were considered in formulating the EULAR recommendations for the management of FM and may be counted in the clinical practice depending on questions of cost, availability, and patient preference (9).

Table I. Main methods of ozone treatment used in patients with FM.

Administration route	Method	Characteristics
Rectal (21, 22)	Insufflation	A given amount of an oxygen/ozone gas mixture is administered through a thin, soft polymeric catheter.
Intravenous (22-27)	Infusion	*Ex vivo* static mode (major autohemotherapy, MaAHT). Up to 250 mL of venous blood is bubbled with an oxygen/ozone gas mixture before being immediately re-administered to the sampled subject. *In vivo* dynamic mode. Ozone is added to infusion solutions before their administration.
Intramuscular (27)		An oxygen/ozone gas mixture is combined with up to 10 mL of venous blood, which is then injected into the muscle (minor auto-hemotherapy, MiAHT).

Oxigen/ozone gas therapy and its mechanism of action in FM

Oxygen/ozone gas therapy (ozone therapy) is a unique form of complementary medicine that seeks to enhance overall health and wellness by introducing ozone gas into the body. Although its specific mechanisms of action are complex and not yet fully understood, it has been shown that it stimulates the immune system, enhances the delivery of oxygen to cells, activates anti-oxidant systems, reduces inflammation, and promotes tissue repair (9). Ozone therapy has been widely investigated in the context of FM, other pain syndromes, and neuroinflammatory and neurodegenerative diseases, and may improve symptoms such as pain, fatigue, and sleep disturbances by increasing tissue oxygen delivery, thus enhancing cell metabolic activity, and improving immune function and tissue repair (10). In addition, it acts as an oxidant and is capable of killing bacteria, viruses, and fungi possibly by interacting with their outer membranes (11), which could be particularly beneficial when treating various infections, especially those resistant to traditional antibiotics (12). In the case of inflammatory arthritis, it is believed that ozone therapy reduces inflammation, improves blood supply, and promotes the regeneration of cartilage cells, and the potent anti-inflammatory effects of ozone gas may help reduce swelling, redness, and pain. Furthermore, improved blood flow to the affected joints may promote the delivery of nutrients and oxygen to the area and aid tissue repair (13). Another intriguing aspect of ozone therapy is that it may stimulate the production of cytokines, lymphocytes, and other immune cells that can help fight infections, reduce inflammation, and promote tissue repair (14).

The anti-inflammatory and anti-oxidant potential of medical ozone is due to the ozone-generated lipoperoxide known as 4-hydroxynonenal (4-HNE)35, a hormetic hallmark of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), FM, musculoskeletal pain, and fatigue, Tirelli *et al*. has found that the use of oxygen/ozone major autohemotherapy (O2/O3-MaAHT) reduced pain and fatigue, and restored good health (15). Ozone also has a beneficial effect on mitochondrial function and immune physiology, and therefore hormetically modulates the immune surveillance of complex painful diseases (15).

Neuro-inflammation (inflammation of the brain or spinal cord tissue) has been linked with various neurological conditions (including Alzheimer's disease, Parkinson's disease, and multiple sclerosis), and recent studies have shown that ozone therapy reduces neuroinflammation by decreasing the brain levels of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-alpha and interleukin (IL)-1 beta, and improving overall brain function (16, 17). It has been found that ozone therapy also has a neuroprotective effect as it increases the activity of anti-oxidant enzymes such as superoxide dismutase and catalase, which can help to protect the brain from the damage of oxidative stress (18-20).

Main studies assessing the efficacy of ozone therapy in FM

Hidalgo-Tallón *et al*. found that rectal ozone insufflation primarily acts on the physical symptoms of FM as it led to a clinically significant improvement in overall severity and pain scores. Interestingly, it was also found that depression significantly improved in 47% of the treated patients, although it was not clear whether this was a direct result of ozone treatment or reflected the overall improvement in well-being. The most common side effect was meteorism (gas in the digestive system) lasting 1-2 days after ozone sessions (21).

Tirelli's 2019 study of 65 patients showed that ozone therapy significantly improved FM symptoms in 70% of cases: *i.e*., almost three-quarters of the patients experienced relief from pain and/or fatigue, with female patients re-

Table II. Main studies about ozone therapy in FM and their findings.

First Author	Year	Patients	Type of Treatment	O2/O3 Concentration	No. of Treatments	Results
Hidalgo Tallón (21)	2013	36	RI	200 mL of gas; concentration 40 µg/mL	Five days a week for 2 weeks, then once weekly	Significant improvement in physical symptoms and depression.
Tirelli (22)	2019	65	RI/MaAHT	10 RI and 55 MaAHT according to SIOOT protocols.	Twice weekly for a month, then twice monthly maintenance treatment.	45 (70%) showed significant (>50%) improvement in symptoms.
Moreno-Fernández (24)	2019	20	MaAHT	150 mL of patient's blood plus 150 mL of O3, gradually increasing to a concentration of 30 µg/mL.	10 sessions (2 a week)	Significant decrease in tender points and FIQ score, and a decrease in oxidative stress and serotonin levels.
Gazioğlu Türkyilmaz (25)	2019	40	MaAHT	100 mL of patient's blood plus 100 mL of O3; concentration 45 vg/mL.	13 sessions (two a week for 5 weeks followed by one a month for 3 months)	Consistent improvement in FIQ and SF-36 scores throughout.
Tirelli (23)	2022	200	MaAHT	200 mL of patient's blood plus 200 mL of O3; concentration 45 µg/mL.	3-4 cycles of 3 or 4 MaAhT sessions)	After one month, 76% showed considerable improvements in function, pain, sleep, mood, and fatigue.
Shen (26)	2022	103 (53 O3-MaAHT; 50 controls)	MaAHT	100 mL of patient's blood plus 100 mL of O3; concentration 20-40 µg/mL	Thrice weekly for 3 weeks	Improvements in sleep, pain intensity, mood, and fatigue.
Sucuoğlu (27)	2023	54 (26 treated, 28 placebo controls)	MaAHT/ MiATH twice weekly	ND	10 sessions	Improvement in FIQ subscale scores (feeling good, fatigue, and sleep quality

RI: rectal insufflation; MaAHT: major oxygen/ozone autohemotherapy; SIOOT: Società Scientifica di Ossigeno-Ozono Terapia; FIQ: Fibromyalgia Impact Questionnaire; MiAHT: minor oxygen/ozone autohemotherapy; ND: not determined.

sponding better than males (22).

One hypothesis concerning the mechanism of action of ozone is based on evidence showing that FM is closely related to oxidative stress and mitochondrial dysfunction. In 2002 Tirelli *et al*. conducted a study among 200 FM patients and showed the almost complete rehabilitation of musculoskeletal function and general arthralgia in 76% of patients one month after O2/O3-MaAHT (23). A more recent report, among 20 subjects, found a significant reduction in tender point and Fibromyalgia Impact Questionnaire (FIQ) scores and a decrease in oxidative stress levels after 10 sessions of ozone MaAHT. All the treated patients experienced improvements in sleep and mental attention, a marked decrease in asthenia, and a moderate increase in serotonin levels (24) Also the study from Gazioğlu Türkyılmaz *et al*. in 2021 showed a significant improvement in FIQ scores as well as in all of the 36-Item Short Form Survey (SF-36) sub-dimensions after 10 MaAHT sessions in 40 patients, but the absence of a control group limited the strength of the evidence (25).

Shen's 2022 study examined the efficacy and safety of combining pharmacological therapy with ozone AHT in patients with insomnia and myofascial pain syndrome, common features of FM, as the anti-oxidant and anti-inflammatory properties of ozone may improve tissue oxygen supply and thus play a role in alleviating symptoms. The results showed that drug therapy alone only partially and temporarily improved insomnia symptoms, whereas combined MaAHT and drug therapy led to more striking short-term improvements in a broader range of symptoms and more sustained incremental effects (26).

Sucuoğlu *et al*. assessed the efficacy of adjunctive ozone therapy using the FIQ, the Pittsburgh Sleep Quality Index, and the 12-item Short-Form Health Survey. Ozone therapy improved some symptoms of FM and the quality of sleep, but there was no significant difference in the total FIQ score between the treatment and the control group. Rectal insufflation led to slight meteorism, and one case of transient hypotension was observed during MaAHT, but there were no complications or side effects in the other participants (27).

The above studies varied in terms of their treatment modalities, the number of patients, ozone concentrations, and the presence/absence of a control group. The controlled study by Sucuoğlu *et al*. used both major and

minor AHT, whereas the study by Shen *et al*. combined ozone and pharmacological therapy with the control group receiving only the latter. The ozone concentrations varied from study to study: Tirelli *et al*. administered 40 μg/mL, Moreno-Fernández *et al*. administered concentrations ranging from 30 to 60 μg/mL, and Shen et al. increased the ozone concentration from 20 μg/mL in the first week to 40 μg/mL in the third week. Table I showed the main techniques of administration used in patients with FM while Table II represents an overview of the cited studies.

Conclusions

One of the main problems facing FM patients is the lack of effective treatments (1). The drugs often offered for symptomatic treatment can sometimes exacerbate the disease as a result of side effects: for example, the widely used painkiller amitriptyline can induce mitochondrial dysfunction and oxidative stress, thus making them unsuitable for patients already suffering from these conditions (28). However, in a such complex disease, clinicians should offer the best treatment, including the use of non-pharmacological therapies, in order to ameliorate the quality of life of these patients (29, 30). Ozone therapy may affect FM by means of various mechanisms:

- Ozone reacts with polyunsaturated fatty acids (PUFAs) to produce reactive oxygen species (ROS) and lipid ozonation products (LOPs), which are significant in ozone biotransformation (31).
- Ozone therapy can lead to redox homeostasis, nitric oxide, calcium, and cytokine homeostasis, and improve oxygen metabolism (32).
- Ozone therapy can reduce the high oxidative stress levels typically observed in FM patients, thus potentially alleviating FM symptoms (26).
- Ozone can stimulate the immune system, thus enhancing its ability to fight infections and heal damaged tissue. This is particularly beneficial for FM patients, who might have impaired immune function (33).
- Ozone therapy enhances the body's use of oxygen, thus improving cell function and overall health. This could help alleviate fatigue, a common symptom of FM and other musculoskeletal disorders. (34, 35).

Adverse reactions to ozone therapy are typically mild and transient, which supports the idea that ozone therapy is generally well-tolerated. The most common side effect reported is meteorism (gas in the digestive system) lasting 1-2 days after ozone sessions (21, 27).

Thus, given a good safety profile, the reported studies would seem to support the use of ozone therapy in the management of FM. However, a number of important points need to be considered:

- The study samples are relatively small, which limits the generalisability of their findings; larger-scale studies are needed to confirm what must be considered preliminary results.
- The various treatment protocols used make it difficult to compare the study results.
- The lack of long-term follow-up data prevents any conclusions concerning the benefits of ozone therapy over time.
- As none of the studies were double-blinded, there is a risk of potential biases.
- The studies relied on subjective measures of symptoms, which can be influenced by various factors, including the placebo effect, although the control groups in the studies by Shen *et al*. and Sucuoğlu and Soydaş strengthen the validity of their findings (26, 27).

In conclusion, the studies suggest that ozone therapy may play a role in the treatment of FM, but further research is needed to address their limitations. Future studies should have larger samples and standardised treatment protocols, be double-blinded, use objective measures of symptoms, and provide long-term follow-up data.

References

1. GALVEZ-SÁNCHEZ CM, REYES DEL PASO GA: Diagnostic Criteria for Fibromyalgia: Critical Review and Future Perspectives. *J Clin Med* 2020; 9(4): 1219. https://www.doi.org/10.3390/jcm9041219
2. VASILEIOS P, STYLIANI P, NIFON G, PAVLOS S, ARIS F, IOANNIS P: Managing fibromyalgia with complementary and alternative medical exercise: a systematic review and meta-analysis of clinical trials. *Rheumatol Int* 2022; 42(11): 1909-23 https://www.doi.org/10.1007/s00296-022-05151-y
3. CASSISI G, SARZI-PUTTINI P: Consistency between the 2016 ACR criteria and a previous diagnosis or hypothesis of fibromyalgia in a specialised referral clinic. *Clin Exp Rheumatol* 2023; 41(6): 1283-91. https://www.doi.org/10.55563/clinexprheumatol/mopepq
4. 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://www.doi.org/10.1038/s41584-020-00506-w
5. MACFARLANE GJ, KRONISCH C, DEAN LE *et al*.: EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis* 2017; 76(2): 318-28. https://www.doi.org/10.1136/annrheumdis-2016-209724
6. CLAUW D, SARZI-PUTTINI P, PELLEGRINO G, SHOENFELD Y: Is Fibromyalgia an Autoimmune Disorder? *Autoimmun Rev* 2024; 23(1): 103424. https://www.doi.org/10.1016/j.autrev.2023.103424
7. ARIANI A, MANARA M, FIORAVANTI A *et al*.: The Italian Society for Rheumatology clinical practice guidelines for the diagnosis and management of knee, hip and hand osteoarthritis. 2019; 71(S1): 5-21. https://www.doi.org/10.4081/reumatismo.2019.1188
8. PERROT S, RUSSELL IJ: More Ubiquitous Effects from Non-Pharmacologic than from Pharmacologic Treatments for Fibromyalgia Syndrome: A Meta-Analysis Examining Six Core Symptoms. *Eur J Pain* 2014; 18(8): 1067-80. https://www.doi.org/10.1002/ejp.564
9. CHIRUMBOLO S, FRANZINI M, PANDOLFI S, TIRELLI U, VALDENASSI L: Commentary: Ozone Therapy as a Novel Complementary Therapeutic Approach in Refractory Idiopathic Granulomatous Mastitis. *Front Med* (Lausanne) 2023; 10: 1272059. https://www.doi.org/10.3389/fmed.2023.1272059
10. SERRA MEG, BAEZA-NOCI J, MENDES ABDALA CV, LUVISOTTO MM, DALLAZEM BERTOL C, ANZOLIN AP: The role of ozone treatment as integrative medicine. An evidence and gap map. *Front Public Health* 2023; 10: 1112296. https://www.doi.org/10.3389/fpubh.2022.1112296
11. GHALEH HEG, IZADI M, JAVANBAKHT M *et al*.: Cytokine Profile and Antioxidants Status in the Moderate and Severe COVID-19 Patients: A Trial of Ozone Therapy Impact as a Medicinal Supplement. *Inflammopharmacology* 2023; 31(6): 3029-36. https://www.doi.org/10.1007/s10787-023-01288-9
12. BIAŁOSZEWSKI D, KOWALEWSKI M: Superficially, Longer, Intermittent Ozone Therapy in the Treatment of Chronic, Infected Wounds. *Ortop Traumatol Rehabil* 2003; 5(5): 652-8.
13. SCONZA C, DI MATTEO B, QUEIRAZZA P *et al*.: Ozone Therapy versus Hyaluronic Acid Injections for Pain Relief in Patients with Knee Osteoarthritis: Preliminary Findings on Molecular and Clinical Outcomes from a

Randomized Controlled Trial. *Int J Mol Sci* 2023; 24(10): 8788. https://www.doi.org/10.3390/ijms24108788
14. CABIOĞLU N, CETIN AKTAS E, EMIROĞLU S *et al*.: Ozone Therapy Restores Immune Dysfunction in Refractory Idiopathic Granulomatous Mastitis as a Novel Potential Therapeutic Approach. *Cell Biol Int* 2023; 47(1): 228-37. https://www.doi.org/10.1002/cbin.11953
15. TIRELLI U, FRANZINI M, VALDENASSI L *et al*.: Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Greatly Improved Fatigue Symptoms when Treated with Oxygen-Ozone Autohemotherapy. *J Clin Med* 2021; 11(1): 29-37. https://www.doi.org/10.3390/jcm11010029
16. SHOHAG S, AKHTER S, ISLAM S *et al*.: Perspectives on the Molecular Mediators of Oxidative Stress and Antioxidant Strategies in the Context of Neuroprotection and Neurolongevity: An Extensive Review. *Oxid Med Cell Longev* 2022; 2022: 7743705. https://www.doi.org/10.1155/2022/7743705
17. BETTE M, CORS E, KRESSE C *et al*.: Therapeutic Treatment of Superoxide Dismutase 1 (G93A) Amyotrophic Lateral Sclerosis Model Mice with Medical Ozone Decelerates Trigeminal Motor Neuron Degeneration, Attenuates Microglial Proliferation, and Preserves Monocyte Levels in Mesenteric Lymph Nodes. *Int J Mol Sci* 2022; 23(6): 3403. https://www.doi.org/10.3390/ijms23063403
18. CAI HA, TAO X, ZHENG LJ *et al*.: Ozone Alleviates Ischemia/Reperfusion Injury by Inhibiting Mitochondrion-Mediated Apoptosis Pathway in SH-SY5Y Cells. *Cell Biol Int* 2020; 44(4): 975-84. https://www.doi.org/10.1002/cbin.11294
19. KUCUKGUL A, ERDOGAN S, GONENCI R *et al*.: Beneficial Effects of Nontoxic Ozone on H2O2-Induced Stress and Inflammation. *Biochem Cell Biol* 2016; 94(6): 577-83. https://www.doi.org/10.1139/bcb-2016-0033
20. NASEZADEH P, SHAHI F, FRIDONI M, SEYDI E, IZADI M, SALIMI A: Moderate O3/O2 Therapy Enhances Enzymatic and Non-Enzymatic Antioxidant in Brain and Cochlear That Protects Noise-Induced Hearing Loss. *Free Radic Res*; 51(9-10): 828-37. https://www.doi.org/10.1080/10715762.2017.1381695
21. HIDALGO-TALLÓN J, MENÉNDEZ-CEPERO S, VILCHEZ JS, RODRÍGUEZ-LÓPEZ CM, CALANDRE EP: Ozone therapy as add-on treatment in fibromyalgia management by rectal insufflation: an open-label pilot study. *J Altern Complement Med* 2013; 19(3): 238-42. https://www.doi.org/10.1089/acm.2011.0739
22. TIRELLI U, CIRRITO C, PAVANELLO M, PIASENTIN C, LLESHI A, TAIBI R: Ozone therapy in 65 patients with fibromyalgia: an effective therapy. *Eur Rev Med Pharmacol Sci* 2019; 23(4): 1786-8. https://www.doi.org/10.26355/eurrev_201902_17141
23. TIRELLI U, FRANZINI M, VALDENASSI L, PANDOLFI S, TAIBI R, CHIRUMBOLO S: Fibromyalgia Treated with Oxygen-Ozone Auto-Haemotherapy (O2-O3-AHT): A Case Study on 200 Patients with a Modified 10-PI-NRS Evaluation. *Eur Rev Med Pharmacol Sci* 2022; 26(21): 7974-9. https://www.doi.org/10.26355/eurrev_202211_30150
24. MORENO-FERNÁNDEZ A, MACÍAS-GARCÍA L, VALVERDE-MORENO R *et al*.: Autohemotherapy with ozone as a possible effective treatment for Fibromyalgia. *Acta Reumatol Port* 2019; 44(3): 244-9.
25. GAZIOĞLU TÜRKYILMAZ G, RUMELI Ş, BAKIR M: Effects of Major Ozone Autohemotherapy on Physical Functionality and Quality of Life in Fibromyalgia Syndrome: A Prospective Cross-sectional Study. *Altern Ther Health Med* 2021; 27(5): 8-12.
26. SHEN W, LIU N, JI Z *et al*.: Combining Ozonated Autohemotherapy with Pharmacological Therapy for Comorbid Insomnia and Myofascial Pain Syndrome: A Prospective Randomized Controlled Study. *Pain Res Manag* 2022; 2022: 3562191. https://www.doi.org/10.1155/2022/3562191
27. SUCUOĞLU H, SOYDAŞ N: Efficacy of Ozone Therapy as an Add-On Treatment in Fibromyalgia: A Randomized Double-Blind Placebo-Controlled Study. *J Back Musculoskelet Rehabil* 2023; 36(2): 357-66. https://www.doi.org/10.3233/BMR-210368
28. MORENO-FERNÁNDEZ AM, CORDERO MD, GARRIDO-MARAVER J *et al*.: Oral treatment with amitriptyline induces coenzyme Q deficiency and oxidative stress in psychiatric patients. *J Psychiatr Res* 2012; 46(3): 341-5. https://www.doi.org/10.1016/j.jpsychires.2011.11.002
29. DI CARLO M, BECI G, CIPOLLETTA E, SALAFFI F: Predicting acupuncture efficacy in fibromyalgia: results of a pragmatic open-label study. *Clin Exp Rheumatol* 2023; 41(6): 1254-61. https://www.doi.org/10.55563/clinexprheumatol/1xr38b
30. GIORGI V, BAZZICHI L, BATTICCIOTTO A *et al*.: Fibromyalgia: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(6): 1205-13. https://www.doi.org/10.55563/clinexprheumatol/257e99
31. BOCCI VA: Scientific and Medical Aspects of Ozone Therapy. State of the Art. *Arch Med Res* 2006; 37(4): 425-35. https://www.doi.org/10.1016/j.arcmed.2005.08.006
32. CHIRUMBOLO S, VALDENASSI L, TIRELLI U *et al*.: The Oxygen-Ozone Adjunct Medical Treatment According to the Protocols from the Italian Scientific Society of Oxygen-Ozone Therapy: How Ozone Applications in the Blood Can Influence Clinical Therapy Success via the Modulation of Cell Biology and Immunity. *Biology* (Basel) 2023; 12(12): 1512. https://www.doi.org/10.3390/biology12121512
33. INGUSCIO CR, CISTERNA B, LACAVALLA MA *et al*.: Ozone and Procaine Increase Secretion of Platelet-Derived Factors in Platelet-Rich Plasma. *Eur J Histochem* 2023; 67(4): 3879. https://www.doi.org/10.4081/ejh.2023.3839
34. SEYAM O, SMITH NL, REID I, GANDHI J, JIANG W, KHAN SA: Clinical Utility of Ozone Therapy for Musculoskeletal Disorders. *Med Gas Res* 2018; 8(3):103-110. https://www.doi.org/10.4103/2045-9912.241075
35. DE SIRE A, AGOSTINI F, LIPPI L *et al*.: Oxygen-Ozone Therapy in the Rehabilitation Field: State of the Art on Mechanisms of Action, Safety and Effectiveness in Patients with Musculoskeletal Disorders. *Biomolecules* 2021; 11(3): 356. https://www.doi.org/10.3390/biom11030356