Review

Oxygen-ozone autohaemotherapy in fibromyalgia: oxidative stress, Nrf2 activation, small fibre neuropathy and a critical narrative review of the evidence

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ABSTRACT

Fibromyalgia (FM) is a chronic pain disorder marked by widespread pain and significant impairment of daily life. Despite evolving diagnostic criteria and recognition as a primary chronic pain condition, current treatments yield limited success, and underlying mechanisms remain under investigation.

This narrative review focuses on oxygen-ozone autohaemotherapy (O_2-O_3-AHT) as a potential intervention for FM, evaluating its biological rationale and possible mechanisms of action. The therapeutic interest in O_2-O_3-AHT centres on its capacity to activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, reduce oxidative stress, improve mitochondrial function, and address small fibre pathology. The review employed a structured narrative synthesis, adhering to SANRA guidelines to ensure methodological rigor and transparency. Comprehensive literature searches included peer-reviewed articles published in English from 2015 to 2025.

Evidence suggests that O_2-O_3-AHT may provide multi-target benefits for FM patients by modulating redox balance, enhancing mitochondrial resilience, and potentially alleviating neuropathic components related to small fibre dysfunction. Clinical studies, though limited and often heterogeneous, report improvements in pain, sleep quality, fatigue, and overall functional status in FM patients treated with O_2-O_3-AHT. Biomarker analyses further support reduced oxidative stress and inflammatory mediators post-intervention. However, the variability in treatment protocols, sample sizes, and outcome measures across studies complicates definitive conclusions about efficacy and safety.

O_2-O_3-AHT represents a promising, mechanism-based approach to FM management, particularly for patients unresponsive to conventional therapies. Its ability to target central and peripheral biological processes aligns with the complex pathophysiology of FM. However, the current evidence base is restricted by methodological inconsistencies and a paucity of large, high-quality randomised trials. Future research should prioritise standardised protocols, robust clinical endpoints, and long-term safety assessment to validate the role of O_2-O_3-AHT in FM treatment. Until then, its use should be considered experimental and guided by careful patient selection and monitoring.

Introduction

Fibromyalgia (FM) is a chronic pain syndrome characterised by widespread musculoskeletal pain, fatigue, sleep disturbance, cognitive dysfunction, and a broad spectrum of somatic and psychological symptoms (1).

Affecting approximately 2–4% of the general population, FM represents a major cause of disability and healthcare utilisation worldwide (2). The disorder predominantly affects women and is frequently associated with mood disorders, autonomic dysfunction, and reduced quality of life (3).

The conceptualisation of FM has evolved substantially over the past three decades. Initially defined through tender point examination by the American College of Rheumatology (ACR) in 1990 (4), diagnostic criteria progressively shifted toward symptom-based frameworks in 2010 and 2016, acknowledging the multidimensional nature of the syndrome and its frequent

coexistence with other conditions. More recently, FM is recognised as a *chronic primary pain* and classified as such in ICD-11, recognising its nociplastic character and central nervous system dysregulation (5).

Despite advances in classification and understanding, therapeutic outcomes remain suboptimal. Approved pharmacological treatments (such as pregabalin, duloxetine, and milnacipran) achieve clinically meaningful benefit in fewer than half of patients, underscoring the need for mechanism-based, multi-target approaches (6). Increasing attention has therefore focused on biological processes that may unify peripheral and central components of FM, including oxidative stress, mitochondrial dysfunction, neuroinflammation, and small fibre pathology (7-10).

Within this context, oxygen-ozone autohaemotherapy (O_2-O_3-AHT) has emerged as a controversial but mechanistically intriguing intervention. This narrative review critically examines the biological rationale for O_2-O_3-AHT in FM, with particular emphasis on hormetic activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway and explores how this mechanism may intersect with oxidative stress, mitochondrial dysfunction, and peripheral small fibre pathology.

Methods

This narrative review was conducted in accordance with established methodological standards for narrative syntheses, with particular attention to the Scale for the Assessment of Narrative Review Articles (SANRA) (11), in order to ensure transparency, scientific rigor, and reproducibility. The review design, literature identification, synthesis approach, and reporting were structured to explicitly address the six SANRA domains: (1) justification of the article's importance, (2) clarity of aims and research questions, (3) description of the literature search strategy, (4) referencing quality, (5) scientific reasoning, and (6) appropriate presentation of data.

Review design and objectives

The review was conceived as a focused narrative synthesis aimed at critically integrating contemporary evidence on the O_2-O_3-AHT in FM, emphasising mechanistic insights, clinical relevance, and translational implications. Clear and predefined objectives guided the review process, specifying the population, phenomena of interest, and conceptual framework to be addressed. This approach was chosen to allow contextual interpretation and theoretical integration of heterogeneous evidence that would not be adequately captured through a purely systematic methodology.

Literature search strategy

A comprehensive and structured literature search was performed across major biomedical databases, including PubMed/MEDLINE, Scopus, and Web of Science. Searches were conducted using a combination of controlled vocabulary terms (*e.g.* MeSH, where applicable) and free-text keywords related to the core concepts of the review. Boolean operators ("AND", "OR") were applied to refine search sensitivity and specificity. The search strategy was iteratively refined to ensure completeness and relevance and was limited to peer-reviewed articles published within 2015 and 2025 relevant to the review objectives. Only articles published in English were considered.

Study selection and eligibility

Titles and abstracts retrieved from the search were screened for relevance to the predefined aims. Full-text articles were subsequently assessed for eligibility based on conceptual relevance, methodological soundness, and contribution to the scientific argument of the review. Both original research articles and high-quality secondary literature (including systematic reviews, meta-analyses, and authoritative consensus documents) were included when they provided substantive mechanistic or clinical insights. Case reports, conference abstracts, and non-peer-reviewed sources were excluded unless they contributed essential contextual information.

Data extraction and narrative synthesis

Relevant data were extracted manually and organised thematically. Rather than aggregating results quantitatively, findings were synthesised using a structured narrative approach, emphasising biological plausibility, consistency across studies, and integration of preclinical and clinical evidence. Conflicting findings were explicitly addressed and critically discussed. Results for the selected publications have been divided into 8 different topics of interest: 1. Fibromyalgia as a multisystem disorder; 2. Oxidative stress and mitochondrial dysfunction in fibromyalgia; 3. Linking oxidative stress to small fibre pathology; 4. Nrf2: master regulator of redox homeostasis; 5. Hormesis and ozone biology; 6. Oxygen-ozone autohaemotherapy: Mechanisms of action; 7. Clinical evidence in fibromyalgia; 8. Safety consideration (Table I).

Quality assurance and SANRA compliance

Throughout the manuscript preparation, explicit alignment with SANRA criteria was maintained. References were selected to ensure accuracy, balance, and contemporaneity. Arguments were developed logically and supported by appropriate citations. Limitations inherent to narrative methodologies were acknowledged. This structured approach was adopted to maximise the scientific credibility and educational value of the review while preserving the interpretative strengths of narrative synthesis.

In the revised version, the Methods section has been expanded with an explicit paragraph clarifying how evidence was weighted: mechanistic and preclinical findings are distinguished from clinical data; high-quality secondary literature (systematic reviews, meta-analyses, randomised controlled trials) is differentiated from lower-quality observational studies, open-label series, and retrospective reports. Furthermore, in the Clinical Evidence section each cited study is now identified by design type (*e.g.* open-label study, retrospective series, single-arm pilot trial), enabling the reader to appraise the evidence hierarchy directly.

Fibromyalgia as a multisystem disorder

From central sensitisation to nociplastic pain

FM has long been conceptualised as a

Table I. This table summarises the most important results obtained, and described in detail, for each of the 8 selected topics.

Topic	Major scientific contribution	Summary
FM as a multisystem disorder	(12-23)	FM is a nociplastic pain disorder with altered central processing, frequently accompanied by mild small fibre pathology, reflecting a spectrum arising from combined central and peripheral mechanisms
Oxidative stress and mitochondrial dysfunction in FM	(7, 24-31)	FM is associated with systemic OXI and impaired antioxidant defences, coupled with mitochondrial dysfunction and reduced ATP production, contributing to fatigue, pain severity, and altered nociceptive processing.
Linking oxidative stress to small fibre pathology	(29, 32-39)	OXI induces mitochondrial and redox-mediated dysfunction in sensory neurons, impairing energy metabolism, excitability, and neurotrophic signalling, thereby promoting heterogeneous, predominantly functional small fibre impairment in FM.
Nrf2: master regulator of redox homeostasis	(25, 29, 40-46)	Nrf2 regulates antioxidant, mitochondrial, and anti-inflammatory defences, but in FM its activation is impaired despite OXI, leading to insufficient redox adaptation and associations with greater pain and disability.
Hormesis and ozone biology	(47-49)	Hormesis involves low-dose OXI activating adaptive antioxidant and mitochondrial defences, forming the rationale for controlled medical ozone therapies.
O2O3-AHT action mechanisms	(50-57)	O_2-O_3 AHT generates redox signalling molecules that activate Nrf2, enhance antioxidant and mitochondrial function, and suppress inflammation, without systemic ozone exposure.
Clinical evidence in FM	(58-62)	Limited clinical and biomarker studies suggest O_2-O_3 AHT may improve pain, function, redox balance, and mitochondrial activity in fibromyalgia, but robust randomized controlled trials are lacking.
Safety consideration	[63-65]	Generally safe under protocols; G6PD screening essential; mild adverse effects.

FM: fibromyalgia; O_2-O_3 AHT: oxygen-ozone autohemotreatment; Nrf2: nuclear factor erythroid 2; OXI: oxidative stress.

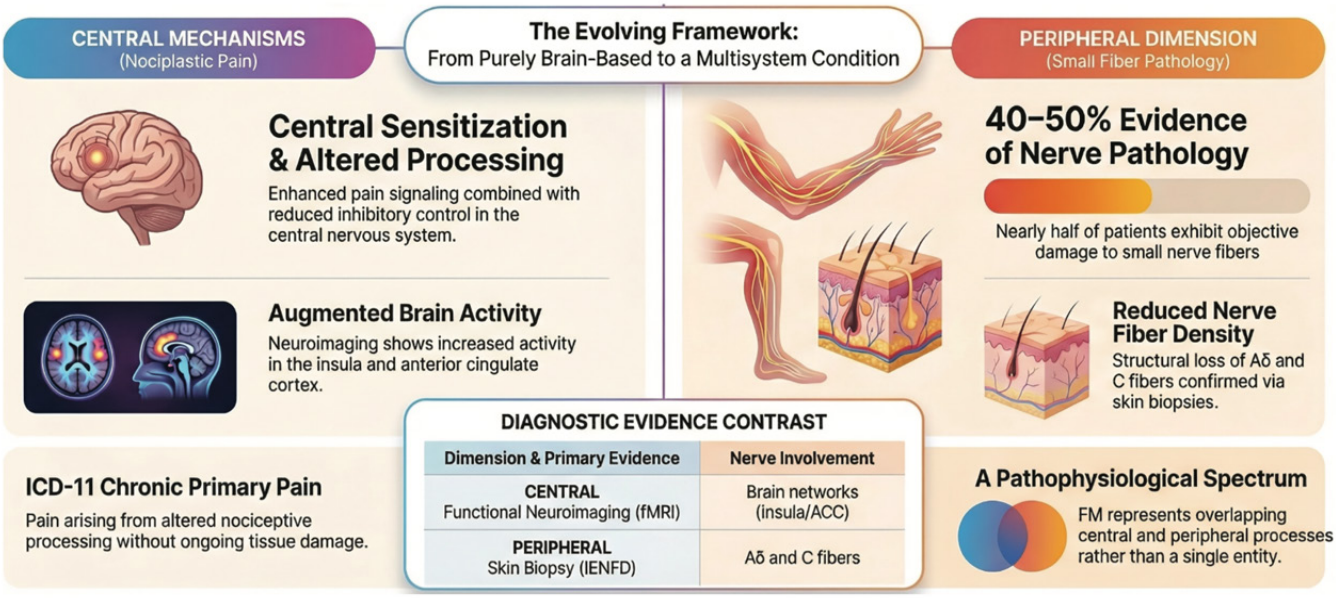


Fig. 1. Contemporary thinking in fibromyalgia research, reflecting the maturation of the field from purely phenomenological descriptions toward mechanistically grounded, heterogeneous models that can guide personalised medicine approaches.
Left side: central mechanisms; right side: peripheral dimensions. The central header establishes the framework's evolution from brain-based to multisystem conceptualisation.
The left part depicts central sensitisation through an anatomical brain illustration highlighting enhanced pain signalling with reduced inhibitory control. Functional neuroimaging evidence shows increased activity in the insula and anterior cingulate cortex, providing objective validation of altered pain processing. These mechanisms are anchored within the ICD-11 definition of Chronic Primary Pain as arising from altered nociceptive processing without ongoing tissue damage.
The right part visually reports the finding that forty to fifty percent of patients show objective nerve pathology. A cross-sectional skin view depicts reduced density of A-delta and C fibres, confirmed via intraepidermal nerve fibre density assessment through skin biopsies.
Overlapping circles at the right end bottom convey that fibromyalgia represents a spectrum where patients may have predominantly central mechanisms, predominantly peripheral pathology, or contributions from both systems in varying proportions.

disorder of central sensitisation, characterised by enhanced nociceptive signal processing, reduced descending inhibition, and altered pain modulation (12, 13). Functional neuroimaging studies demonstrate augmented activity in pain-processing regions, including the insula, anterior cingulate cortex, and somatosensory cortices, alongside altered connectivity within default mode and salience networks (14, 15).

The ICD-11 designation of FM as chronic primary pain reflects a broader nociplastic framework, in which pain arises from altered nociceptive processing rather than ongoing tissue damage or classical neuropathy (16, 17). However, this central model alone fails to explain the full clinical heterogeneity of FM, particularly symptoms suggestive of peripheral nervous system involvement (Fig. 1).

Small fibre pathology: a peripheral dimension

Over the past decade, multiple independent studies have demonstrated that approximately 40–50% of FM patients exhibit objective evidence of small fibre pathology (SFP), affecting thinly myelinated Aδ fibres and unmyelinated C fibres (18-20). Reduced intraepidermal nerve fibre density (IENFD) on skin biopsy and abnormalities on corneal confocal microscopy provide reproducible structural evidence of peripheral nerve involvement (21).

Importantly, the degree of fibre loss in FM is typically milder than in classical small fibre neuropathy, and many patients show normal routine neurological examination (22). This has led to the concept of *partial, heterogeneous, or functional* small fibre involvement, rather than a uniform neuropathy. The coexistence of nociplastic central mechanisms and peripheral small fibre dysfunction suggests that FM may represent a spectrum of overlapping pathophysiological processes rather than a single disease entity (23).

Oxidative stress and mitochondrial dysfunction in fibromyalgia

Evidence of systemic oxidative imbalance

A substantial body of literature indicates that FM is associated with increased oxidative stress and impaired antioxidant defences (7, 24, 25). Elevated levels of lipid peroxidation markers, including malondialdehyde (MDA), and protein oxidation markers such as advanced oxidation protein products (AOPP), have been consistently reported (7, 24, 26). In parallel, total antioxidant capacity (TAC) and the activity of key antioxidant enzymes, superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), are reduced (27, 28).

Disruption of the glutathione redox system appears particularly relevant, with decreased reduced glutathione (GSH), increased oxidised glutathione (GSSG), and a lowered GSH:GSSG ratio (29). These abnormalities correlate with pain severity, fatigue, and functional impairment, supporting a pathophysiological role rather than an epiphenomenon.

Mitochondrial dysfunction and energy deficit

Mitochondrial abnormalities have been documented in FM patients, including reduced complex I activity, impaired mitochondrial membrane potential, and decreased ATP production in peripheral blood mononuclear cells and muscle tissue (30, 31). Given the high energy demands of sensory neurons and central pain-modulating circuits, mitochondrial dysfunction provides a plausible link between oxidative stress, fatigue, and heightened pain sensitivity.

Linking oxidative stress to small fibre pathology

Oxidative stress has been increasingly proposed as a key mechanistic link between systemic metabolic dysregulation and peripheral nervous system involvement in FM (32, 33). Sensory neurons appear particularly susceptible to redox imbalance owing to their exceptionally high mitochondrial density, extended axonal architecture, and limited regenerative capacity (29). In this context, even modest disturbances in oxidative homeostasis may translate into clinically meaningful neuronal dysfunction rather than overt structural loss.

Accumulating evidence indicates that mitochondrial injury within peripheral sensory neurons represents an early and central event in FM pathophysiology. Oxidative damage to mitochondrial DNA and respiratory chain complexes impairs ATP synthesis, disrupts calcium homeostasis, and compromises axonal transport, thereby reducing the ability of small fibres to maintain distal axonal integrity (34). In parallel, reactive oxygen and nitrogen species can directly modify ion channels, cytoskeletal proteins, and membrane lipids, altering excitability and signal transmission without necessarily inducing frank axonal degeneration (35).

Oxidative stress further interferes with neurotrophic signalling pathways critical for neuronal maintenance and plasticity (36). Alterations in nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) signalling have been reported in FM, potentially lowering neuronal resilience to metabolic and inflammatory stressors (37). Moreover, redox imbalance promotes a pro-inflammatory microenvironment through activation of transcriptional regulators such as NF-κB, leading to increased production of cytokines including TNF-α, IL-1β, and IL-6 (38).

Importantly, these converging mechanisms align with the partial and heterogeneous pattern of small fibre pathology described in FM.

Rather than uniform fibre degeneration, oxidative stress-driven processes may induce a state of chronic vulnerability and functional impairment, providing a biologically plausible explanation for symptom fluctuation and interindividual variability observed across patients (39).

Nrf2: master regulator of redox homeostasis

Biology of the Nrf2 pathway

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that orchestrates cellular defence against oxidative and electrophilic stress (40). Under basal conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (Keap1), which targets it for proteasomal degradation. Oxidative or electrophilic modification of critical Keap1 cysteine residues disrupts this interaction, al-

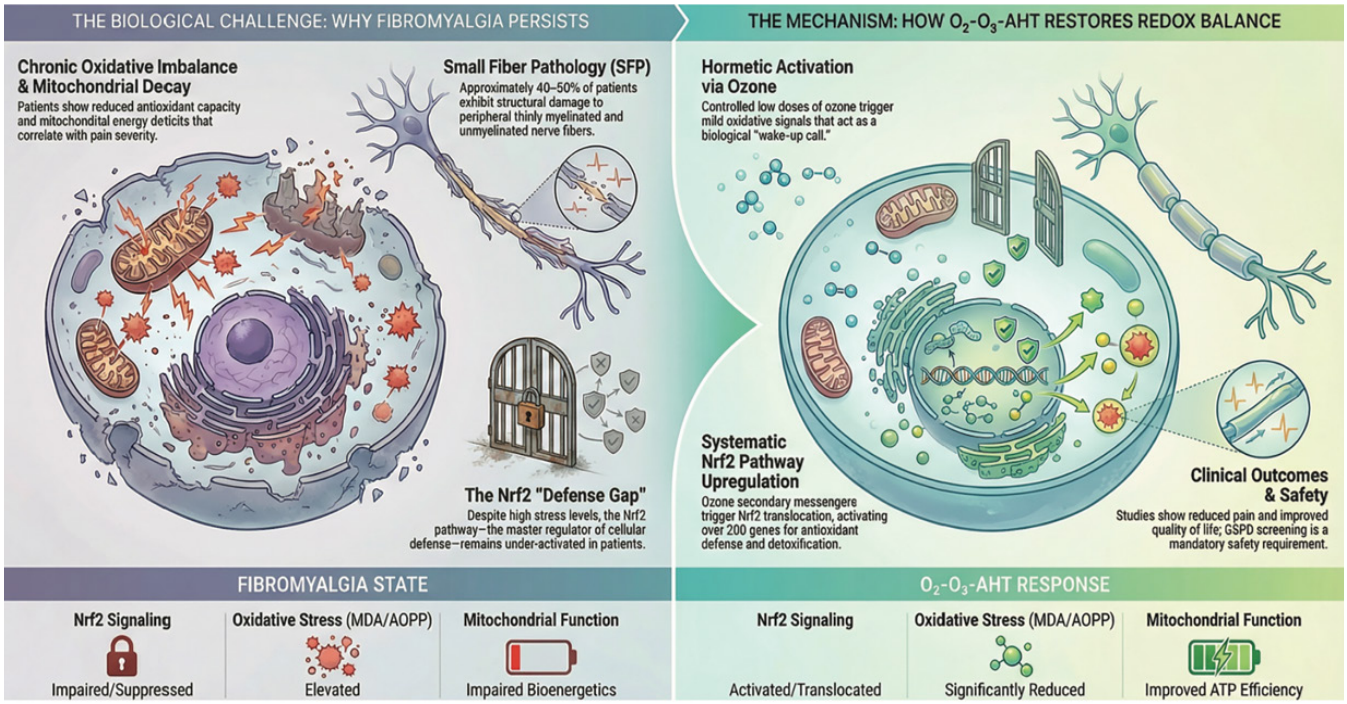


Fig. 2. Mechanistic rationale for oxygen-ozone autohaemotherapy (O_2-O_3-AHT) as a therapeutic intervention in fibromyalgia syndrome. The visual narrative shows how this treatment addresses fundamental pathophysiological disruptions at the cellular level.
Left panel depicts three interconnected pathological features characteristic of fibromyalgia. Chronic oxidative imbalance and mitochondrial decay result in reduced antioxidant capacity and impaired cellular energy production, directly correlating with clinical pain severity. Small fibre pathology, affecting 40–50% of patients, manifests as structural damage to peripheral thinly myelinated and unmyelinated nerve fibres. Central to the dysfunction is the insufficient activation of Nrf2 pathway (herein defined as 'Nrf2 Defence Gap') despite elevated stress levels, the Nrf2 pathway remains paradoxically suppressed, leaving the cellular antioxidant defence system inadequately activated.
Right panel illustrates how controlled low-dose ozone exposure functions as a biological 'wake-up call' through hormetic activation. Ozone-derived secondary messengers trigger Nrf2 translocation to the nucleus, systematically upregulating over 200 genes involved in antioxidant defence and detoxification pathways. This cascade effect triggers cellular redox homeostasis, improves mitochondrial ATP efficiency, and significantly reduces oxidative stress markers like malondialdehyde and Advanced Oxidation Protein Products (MDA/AOPP).
In the lower part of the figure the clinical translational perspective is summarised in the comparative biomarker panels, showing the transition from impaired to activated Nrf2 signalling, elevated to normalised oxidative stress, and compromised to improved mitochondrial bioenergetics.

lowing Nrf2 to accumulate, translocate to the nucleus, and bind antioxidant response elements (AREs) (41, 42). Nrf2 regulates the expression of over 200 genes involved in antioxidant defence, detoxification, mitochondrial biogenesis, proteostasis, and inflammation control, including HO-1, NQO1, glutamate-cysteine ligase, GPx, SOD, catalase, and multiple glutathione-related enzymes (43, 44). Nrf2 plays a pivotal role in aging neurodegenerative disorders as well as neuropathic pain (45).

Nrf2 dysfunction in fibromyalgia

Emerging evidence suggests that FM patients exhibit impaired Nrf2 signalling despite elevated oxidative stress (25, 29, 45). Reduced nuclear translocation of Nrf2 and suppressed expression of downstream antioxidant enzymes have been observed in peripheral immune cells. Lower Nrf2 activity correlates with higher oxidative stress markers, greater pain intensity, and worse functional outcomes, suggesting a failure of adaptive redox responses as it happens in neurodegenerative disorders and neuropathic pain (29, 46).

Hormesis and ozone biology

Hormesis describes a biphasic dose-response relationship in which low-dose stressors activate adaptive protective mechanisms, whereas high doses are harmful (47, 48). Mild oxidative challenges can upregulate endogenous antioxidant systems, enhance mitochondrial function, and increase cellular resilience. Ozone, a potent oxidant at high concentrations, can function as a hormetic stimulus when administered in controlled, low doses (49). This principle underpins medical ozone applications and is central to understanding the rationale for O_2-O_3-AHT.

Oxygen-ozone autohaemotherapy: mechanisms of action

In O_2-O_3-AHT, a defined volume of autologous blood is exposed *ex vivo* to a precise oxygen-ozone mixture and reinfused intravenously (50, 51). Ozone reacts immediately with plasma constituents, generating secondary messengers such as hydrogen peroxide and lipid ozonation products (LOPs), including 4-hydroxynonenal. These molecules act as redox signals rather than toxins. Importantly, no free ozone enters systemic circulation.

Nrf2 activation

LOPs modify Keap1 cysteine residues, promoting Nrf2 stabilisation and nuclear translocation (53, 53). Additional signalling pathways, including MAPK activation and p62-mediated Keap1 degradation, further amplify Nrf2 signalling (54, 55). The result is a coordi-

nated upregulation of antioxidant and cytoprotective genes over hours to days.

Mitochondrial and anti-inflammatory effects

Nrf2 activation promotes mitochondrial biogenesis and improves bioenergetic efficiency (56), while HO-1 and related pathways suppress NF-κB-driven inflammation (57). These effects align closely with the dominant biological abnormalities observed in FM.

Clinical evidence in fibromyalgia

The clinical evidence base for O_2-O_3-AHT in fibromyalgia currently comprises a small number of open-label studies, retrospective series, and single-arm pilot trials, all of which are characterised by limited sample sizes, variable treatment protocols (differing ozone concentrations, blood volumes, number of sessions, and co-interventions), and inconsistent outcome measures. No adequately powered, double-blind, placebo-controlled randomised trial has been conducted to date.

Open-label reports and retrospective series suggest improvements in pain intensity, Fibromyalgia Impact Questionnaire (FIQ) scores, and quality of life, with effects reported to persist for several months after treatment completion (58, 59). Biomarker analyses demonstrate reductions in oxidative stress markers (MDA, AOPP), increases in total antioxidant capacity and antioxidant enzyme activity, and decreases in inflammatory mediators (60). Improvements in mitochondrial bioenergetics have been reported in peripheral immune cells (61, 62). These findings should, however, be interpreted with caution.

A critical methodological concern shared by virtually all available studies is the absence of blinding. Fibromyalgia outcome measures, pain intensity, fatigue, sleep quality, functional status, are inherently subjective and patient-reported, and are therefore particularly susceptible to placebo and non-specific effects. In the absence of a credible sham procedure, improvements observed in open-label autohaemotherapy studies cannot be reliably distinguished from expectancy effects, regression to the mean, or the benefits of increased therapeutic attention and contact. This limitation substantially constrains the interpretability of reported clinical benefits.

Protocol heterogeneity across studies further limits cross-study comparability. Ozone concentrations, treatment frequencies, blood volumes processed, and concurrent therapies differ substantially between series, precluding meaningful aggregation of results. Reported effect sizes, where computable, should be regarded as preliminary and hypothesis-generating rather than indicative of established efficacy. Definitive conclusions regarding the clinical benefit or disease-modifying potential of O_2-O_3-AHT in fibromyalgia cannot be drawn from the currently available evidence.

Safety considerations

The characterisation of O_2-O_3-AHT as having an "acceptable safety profile" requires important qualification. This assessment is based exclusively on short-term procedural tolerability reported in small, often uncontrolled case series, not on systematic adverse event surveillance, pharmacovigilance-grade monitoring, or long-term follow-up data. In the absence of rigorously designed safety studies, the current evidence base does not permit a definitive assessment of the safety of repeated or prolonged autohaemotherapy.

Reported adverse events are generally mild and procedure-related, including transient fatigue, mild discomfort at the phlebotomy site, and occasional post-infusion malaise. Serious adverse events are rare in published series, but the absence of systematic reporting mechanisms and standardised adverse event monitoring in most studies means that rare or delayed complications may remain undetected. Mandatory screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to treatment is essential, as this enzyme deficiency constitutes an absolute contraindication due to the risk of acute haemolysis (65).

Long-term safety data are largely absent. Several areas of specific uncertainty deserve explicit acknowledgement: (a) the effects of repeated oxidative preconditioning via ozone exposure have not been characterised in prospective longitudinal studies; (b) potential immunomodulatory consequences of repeated autohaemotherapy sessions have not been systematically monitored; and (c) the lack of post-market surveillance registries for ozone therapy in most countries means that rare serious adverse events may remain unreported and unquantified. Until robust long-term safety data are available, O_2-O_3-AHT should be considered investigational, and its use should be accompanied by structured monitoring and careful patient selection.

Future directions

It is important to acknowledge upfront that the biological model advanced in this review, linking oxidative stress, impaired Nrf2 signalling, mitochondrial dysfunction, and small fibre pathology in fibromyalgia, and proposing O_2-O_3-AHT as a mechanistically targeted remedy, constitutes, at present, a coherent working hypothesis rather than an established pathophysiological framework. The causal relationships between Nrf2 hypofunction and fibromyalgia pathophysiology are inferred largely from correlational and cross-sectional data; whether pharmacological or biological correction of Nrf2 signalling would translate into clinically meaningful symptomatic improvement in FM patients remains unproven. Moreover, much of the mechanistic evidence cited is derived from preclinical models or from non-FM chronic pain conditions, and the translational assumptions required to apply these findings to fibromyalgia should be made explicit rather than treated as self-evident.

Fibromyalgia is increasingly recognised as a complex, multisystem disorder characterised by nociplastic pain processing, pervasive oxidative stress, mitochondrial dysfunction, and, in a substantial subset of patients, involvement of small peripheral nerve fibres (66). Within this framework, impaired Nrf2 signalling has been proposed as a potential unifying biological vulnerability, linking redox imbalance, altered cellular resilience, and heightened susceptibility of sensory pathways to metabolic and inflammatory stressors.

Preliminary and exploratory clinical observations and biomarker studies suggest potential symptomatic and biological signals; however, these findings are hypothesis-generating and require confirmation in adequately powered, controlled trials. Symptom improvements reported in open-label studies cannot be unambiguously attributed to the specific ozone-mediated mechanisms proposed, given the absence of mechanistic validation alongside clinical outcome assessment in the same patient cohorts. The current body of evidence remains insufficient to support definitive conclusions regarding efficacy or disease-modifying potential in fibromyalgia.

Future research should prioritise well-designed randomised controlled trials integrating robust clinical endpoints with mechanistic assessments, including redox biomarkers, mitochondrial function, and objective measures of peripheral nerve integrity. Until such data are available, O_2-O_3-AHT should be regarded as an investigational, adjunctive option within a comprehensive, multimodal management strategy for fibromyalgia.

Limitations

This narrative review has several limitations that should be acknowledged when interpreting its findings. First, by design, narrative reviews, even if following the SANRA criteria, do not follow the formal methodological rigor of systematic reviews or meta-analyses, and therefore are inherently susceptible to selection bias and subjective interpretation of the literature. Although efforts were made to identify and critically appraise relevant peer-reviewed studies, the absence of a predefined protocol, quantitative synthesis, and duplicate screening limits reproducibility and precludes formal assessment of publication bias.

Second, the available evidence addressing oxidative stress, mitochondrial dysfunction, small fibre pathology, and redox-modulating interventions in fibromyalgia is heterogeneous and often indirect. Many mechanistic insights are derived from small observational studies, exploratory biomarker analyses, or extrapolation from related chronic pain and neuroinflammatory conditions. As a result, causal relationships cannot be established, and the relative contribution of individual biological pathways remains uncertain.

Third, the clinical literature on oxygen-ozone autohaemotherapy is limited by small sample sizes, variability in treatment protocols, inconsistent outcome measures, and a scarcity of rigorously controlled randomised trials. These factors restrict the generalisability of reported findings and increase the risk of overestimating treatment effects.

Finally, fibromyalgia itself represents a clinically and biologically heterogeneous syndrome. Interindividual variability in symptom profiles, comorbidities, and underlying mechanisms may limit the applicability of unified pathophysiological models and therapeutic hypotheses proposed in this review. Consequently, the conclusions should be viewed as hypothesis-generating rather than definitive, underscoring the need for high-quality, mechanism-informed clinical research.

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