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## THE POTENTIAL OF OZONE THERAPY IN RELIEVING CHRONIC PAIN: AN UPDATED REVIEW

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***Laura Beatriz Morais Leite***

Universidade Potiguar

Natal - Rio Grande do Norte

<https://orcid.org/0000-0002-6870-0762>

***Marianna Pereira Silva Ramalho***

Universidade Potiguar

Natal - Rio Grande do Norte

<https://orcid.org/0009-0005-2182-9728>

***Cecília Maria Tavares Machado***

Universidade Potiguar

Natal - Rio Grande do Norte

<https://orcid.org/0009-0001-3989-6700>

***Clarisse Cleide Fagundes Siqueira Chaves***

Universidade Potiguar

Natal - Rio Grande do Norte

<https://orcid.org/0009-0003-7336-1368>

***Giovana Nunes de Assunção***

Universidade Potiguar

Natal - Rio Grande do Norte

<https://orcid.org/0000-0003-4429-3442>

***Laura Isabel Duarte de Santana***

Universidade Potiguar

Natal - Rio Grande do Norte

<https://orcid.org/0009-0006-1609-3725>

***Taís Holland Queiroz***

Universidade Potiguar

Natal - Rio Grande do Norte

<https://orcid.org/0009-0004-2262-3484>

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***Raquel Pereira de Lima***

Natal - Rio Grande do Norte

<http://lattes.cnpq.br/7957209931252771>

***Valeska Cristina Bulhões de Souza***

Universidade Potiguar

Natal - Rio Grande do Norte

<https://orcid.org/0009-0008-8025-6984>

***Ricardo Ney Cobucci***

Universidade Potiguar

Natal - Rio Grande do Norte

<https://orcid.org/0000-0002-0184-2061>

**Abstract:** OBJECTIVE: To explore and analyze the most recent and relevant studies that address the potential of ozone therapy in relieving chronic pain. METHODS: We used the SciELO and PubMed databases, using the following search strategy: “Ozone Therapy” AND “Chronic Pain”, to carry out this literature review. We included articles in English or Portuguese, published in the last 5 years, and studies relating the application of ozone therapy to chronic pain. 69 articles were found, of which 18 were selected for this study. RESULTS: The results obtained reinforce the growing relevance of ozone therapy as a therapeutic option in various conditions associated with chronic pain, whether in the context of joint diseases, fibromyalgia, low back pain or other musculoskeletal injuries. This is related to ozone’s ability to modulate inflammatory processes, induce oxidative stress and ultimately promote tissue regeneration. CONCLUSION: This study demonstrates that ozone therapy is an effective resource in the management of chronic pain, especially in rheumatological complaints, since it will provide an anti-inflammatory effect and reduce oxidative stress, resulting in pain relief in the short and medium term. However, more studies are needed to develop a safe protocol for the use of ozone therapy in chronic pain.

**Keywords:** Ozone therapy; Chronic pain; Knee osteoarthritis; Low back pain.

## INTRODUCTION

Pain is a sensory and emotional experience that is unpleasant or reminiscent of the sensation caused by actual or potential tissue damage. In this sense, chronic pain is characterized by persistence for a period of more than three months, regardless of the degree of recurrence, intensity and functional or psychosocial implications<sup>1</sup>. Due to the intensity and difficult management of chronic pain, various medications such as analgesics and anti-in-

inflammatories (including corticosteroids) are used, which are often not enough<sup>2</sup>.

In Brazil, chronic pain is one of the greatest demands on primary health care and the cause of referrals to secondary care<sup>2</sup>. This condition is responsible for high public spending on health systems, great incapacitation of individuals of all ages and, consequently, an intense reduction in the quality of life and outlook for the population in general. Musculoskeletal pain is generally related to chronic inflammatory processes and immune hyperactivation, causing functional incapacity in patients<sup>3</sup>.

Given this situation, ozone therapy in medicine is becoming a growing reality, with more and more professionals making use of this therapeutic tool for pain relief, due to its effect on immune and inflammatory modulation<sup>4,5</sup>. The technique is a treatment that uses the oxidative potential of ozone (O<sub>3</sub>), which exerts anti-inflammatory, analgesic and antioxidant actions, involving a gaseous mixture with oxygen, called medical ozone (O<sub>2</sub>O<sub>3</sub>)<sup>(6)</sup>.

Given the potential of ozone therapy and the controversies surrounding its benefits, this study aims to explore and analyze the relationship between its application and the relief of chronic pain.

## **METHODS**

### **STUDY DESIGN**

This integrative literature review was conducted using the SciELO and PubMed databases, using the following search strategy: Ozone Therapy and Chronic Pain. A total of 69 articles were found.

## **DATA ANALYSIS**

The articles studied were selected in two stages: a priori, the studies were identified and screened according to the inclusion and exclusion criteria in the aforementioned databases. In the second stage, the selected studies were read and included in this review. This process is illustrated in the flowchart (Figure 1).

### **INCLUSION AND EXCLUSION CRITERIA**

The filters used for inclusion in the research were: English or Portuguese language; studies such as reviews and clinical trials, publications from the last 5 years, studies relating the application of ozone therapy to chronic pain.

The exclusion criteria adopted include texts with a publication time of more than 5 years (2018-2023), experiments on animals, articles not available in full, studies that are off topic.

### **RISKS AND BENEFITS**

For the scientific community, there is the benefit of expanding knowledge on the subject proposed by the research and encouraging new studies on this topic. In addition, this study can be used as a basis for further discussions on the use of ozone therapy in chronic pain.

As a risk, there is the possibility of misinformation and misinterpretation of the data, events that will be avoided by the researchers themselves constantly reviewing the chosen line of data interpretation.

## **RESULTS AND DISCUSSION**

After applying the authors' inclusion/exclusion criteria, 15 studies were selected, the main results of which are shown in Table 1. The information collected was grouped according to the following structure: author, year, main results, type of study and conclusion.

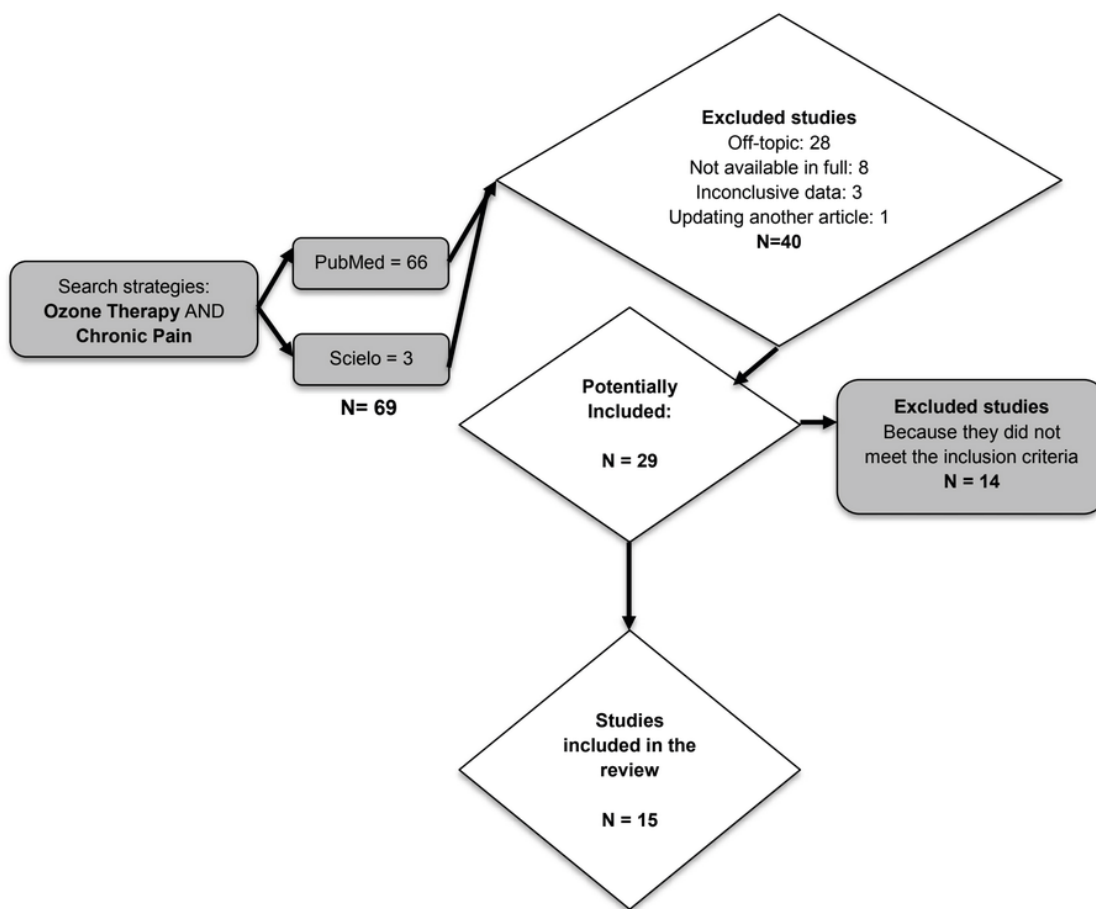


Figure 1: Flowchart of the selection of articles.

AUTHOR (YEAR)	MAIN RESULTS	TYPE OF STUDY	CONCLUSION
Sire A et al. <sup>3</sup> (2022)	In back pain, it reduces the autoimmune inflammatory reaction. In osteoarthritis, it shows promise biochemically and clinically. In rheumatic diseases, it regulates immunity, possibly related to cytokine production. For temporomandibular disorders, it reduces the production of pro-inflammatory cytokines, suggesting benefits in cartilage repair. Ozone therapy is a non-invasive and effective option for managing TMD pain.	Comprehensive Review	Ozone therapy has emerged as an effective therapeutic option in various contexts, demonstrating its ability to modulate inflammatory responses and relieve symptoms associated with conditions such as back pain, osteoarthritis, rheumatic diseases and temporomandibular disorders.
Noori-Zadeh A et al. <sup>9</sup> (2019)	Analysis of the Q and I2% indices indicated high heterogeneity in the selected studies, leading to the choice of the random effects model to calculate the effect size (SMD). The main analysis revealed an SMD of -28.551 (95% confidence interval, -32.553 to -24.549), indicating a significant impact on pain reduction. The P-value for the significance of the combined SMD was 0.000, demonstrating clear statistical significance.	Systematic review and meta-analysis.	The P-value for the significance of the combined SMD was 0.000, demonstrating clear statistical significance. The meta-analysis provides evidence that intra-articular ozone therapy is an effective way of managing chronic pain in OAJ.
Ryska P et al. <sup>18</sup> (2021)	Two cases of non-serious and highly transient complications (nausea and mild headache) were observed in the TFOOT group immediately after the procedure. Both patients recovered fully within 15 minutes, with no residual complaints. An early post-treatment increase in the VAS score was observed in 45 patients: 15 (26.3%) in the PRF group, 20 (29%) in the TFOOT group and 10 (19%) in the TFESI group.	Comparative study	TFESI (corticosteroid with local anesthetic) was the most effective procedure among the treatments examined for reducing early post-treatment pain in patients with chronic lumbar radicular syndrome. However, there were no significant differences between the 3 methods in the long term.

Oliviero A et al. <sup>8</sup> (2019)	Studies were carried out over 1, 3, 6 and 12 months. The data analyzed show that the most promising protocol in reducing pain is the intra-articular injection of 20 µg/mL × 20 mL of O <sub>3</sub> , once a week for four consecutive weeks.	Systematic review	There is agreement that ozone can allow greater mobility of the knee joint, pain relief and a reduction in effusion. There is still controversy over the volumes and concentrations that should be injected. However, studies with adequate power and sufficiently long follow-up are needed to establish which dose(s) and frequency of administration are ideal.
Rowen RJ et al. <sup>4</sup> (2019)	DIV ozone is controversial among ozone practitioners. Its disadvantage is vein irritation (veins have no protection against catalase), and it can induce several minutes of coughing and chest tightness if administered too much and too quickly. However, 250,000 treatments without any significant and lasting adverse effects have been identified except for local vein problems.	Case report	Ozone therapy is very new and novel to conventional medicine. Its researched biochemical mechanisms suggest that it is a worthy consideration for CRPS. Ozone therapy deserves active study in pain centers for the treatment of JRPS and other pain conditions.
Hidalgo-Tallón FJ et al. <sup>5</sup> (2022)	DIV ozone is controversial among ozone practitioners. Its disadvantage is vein irritation (veins have no protection against catalase), and it can induce several minutes of coughing and chest tightness if administered too much and too quickly. However, only local venous problems have been seen.	Literature Review	Non-drug treatments for pain are urgently needed in this era of opioid crisis. Therapy with ozone deserves active study in pain centers for the treatment of JRPS and other pain conditions.
Tirelli U et al. <sup>7</sup> (2019)	We found a significant improvement (>50% of symptoms) in 45 patients (70%). No patient reported significant side effects. In conclusion, it is effective for fibromyalgia patients without significant side effects.	Case studies	At the moment, ozone therapy seems to be a treatment that, also because it has no side-effects, can be offered to fibromyalgia patients who are not getting adequate results from other available treatments and can be considered as complementary/integrative medicine.
Chemehsani A et al. <sup>14</sup> (2023)	The study showed that TFESI was effective for a short period. On the other hand, TFEOI was effective in the short and long term.	One-year retrospective study	The results of this study provide that ozone injection has high benefits in the management of CLBP in the Lebanese population.
Babaei-Ghazani A et al. <sup>17</sup> (2019)	Pain reduction (daily and morning) and improvement in daily activity were better in the corticosteroid group two weeks after injection; however, at 12 weeks, the ozone (O <sub>2</sub> -O <sub>3</sub> ) group had significantly greater improvement (P = 0.003, P = 0.001 and P = 0.017, respectively).	Randomized clinical trial	Both methods were effective in treating chronic PF. Steroid injection provided a faster and shorter-term therapeutic effect. However, ozone (O <sub>2</sub> -O <sub>3</sub> ) injection led to a slower and longer-lasting treatment result. Ozone (O <sub>2</sub> -O <sub>3</sub> ) injection may be an effective treatment with a slow onset and longer durability in the treatment of chronic PF.
Paolucci T et al. <sup>11</sup> (2021)	Intra-group analysis showed that all scores improved over time compared to baseline values and were maintained even 1 month after treatment. No adverse events occurred.	Prospective, observational case-control study	An integrated rehabilitation protocol involving O <sub>2</sub> O <sub>3</sub> injections and mFV for 3 weeks reduces pain, increases autonomy in activities of daily living and strengthens the quadriceps femoris.
Daste C et al. <sup>12</sup> (2021)	Of the 18 eligible trials, five evaluated glucocorticoid (GC) RTDs and were included in a quantitative synthesis; 13 evaluated other products, and were included in a narrative synthesis. The standardized mean differences (95% CI) for GC IDTs for low back pain intensity and activity limitations were -1.33 (-2.34; -0.32) and -0.76 (-1.85; 0.34) in the short term, -2.22 (-5.34; 0.90) and -1.60 (-3.51; 0.32) in the medium term and -1.11 (-2.91; 0.70) and -0.63 (-1.68; 0.42) in the long term, respectively. The odds ratios (95% CI) for serious and minor adverse events with GC IDTs were 1.09 (0.25; 4.65) and 0.97 (0.49; 1.91).	Systematic review and meta-analysis	GC IDTs are associated with a short-term reduction in the intensity of low back pain in people with DLcNS. The positive effects are not sustained. RTDs have no effect on activity limitations. Our conclusions are limited by the high heterogeneity and limited methodological quality among the studies.

Imani F et al. <sup>10</sup> (2020)	The mean WOMAC score of the DS group decreased significantly ( $P < 0.001$ ) sixteen weeks after the intervention. A similar decrease ( $P < 0.001$ ) was observed in the DSO group. The decrease in the WOMAC score at the third and sixteenth weeks after the intervention was significant in the DSO group compared to the DS group ( $P < 0.005$ ).	Randomized, blinded and controlled clinical trial.	For patients with knee OA, prolotherapy with ozone plus hypertonic dextrose and somatropin was more effective in sedating pain and improving knee stiffness and function than dextrose and somatropin alone.
Tirelli U et al. <sup>15</sup> (2022)	A fairly complete rehabilitation of musculoskeletal function and general arthralgia was observed in 76% of patients at one-month follow-up.	Quantitative case study	Oxygen-ozone autohemotherapy represents a formidable therapeutic approach for FM, deserving further studies to fully elucidate the ozone effect in this pathology.
Cantele F et al. <sup>13</sup> (2021)	A significant decrease in NRSp and ODI scores was observed after treatment (T1) (, respectively, $p = 0.03$ and $p = 0.01$ ), while a significant increase was detected for PCS-12 ( $p < 0.01$ ). Six months after the end of treatment (T2), patients were asked to provide a score on their level of NRSp, NRSa and NRSm at that time. ANOVA revealed a significant main effect for the “time” factor ( $p < 0.005$ ).	Retrospective observational study.	People who reported a more compromised psychological well-being due to low back pain had better results after treatment with O2O3. The efficacy of intramuscular to vertebral injections of O2O3 in reducing pain and disability in patients suffering from chronic low back pain was confirmed, and ozone injections are successful in improving the overall perception of physical health.
Hidalgo-Tallón FJ et al. <sup>16</sup> (2023)	After two consecutive sessions, the improvements recorded were remarkable and the tolerability of the treatment was excellent, with the patient reporting feeling “really better”, without any secondary inflammatory reaction, which allowed him to resume his training.	Case report.	Injected medical ozone is effective and well tolerated in the treatment of musculoskeletal pain and can be useful in the treatment of sports injuries and performance recovery.

TABLE 1: Uses of ozone therapy and their respective results.

### OZONE THERAPY

Medical ozone (O3O2) has a composition of 95% oxygen (O2) and 5% ozone (O3), and a short half-life of only 40 minutes at 20°C. For this reason, it cannot be stored and must be produced “in situ” for each application<sup>3,5</sup>. The routes of administration include topical, infiltrative and systemic, and can be used in the form of ozonized oils or water subcutaneously, intramuscularly or intra-articularly, intravenously or autohemotherapy<sup>4,7</sup>.

When O3O2 is applied, the ozone is distributed to the interstitial tissue causing an acute oxidative process, producing hydrogen peroxide (H2O2) and a combination of lipid ozonation products (LOP), which in turn increase catalase and glutathione, causing an activation in the cascades of anti-inflammatory interleukins (IL-1,2,6 and 7). Thus, ozone therapy protects tissues from oxidative damage by stimulating a balance of cytokines, causing a redox balance<sup>5</sup>.

### INTRA-ARTICULAR OZONE THERAPY IN THE KNEE

Osteoarthritis (OA) is a chronic and degenerative joint disease, which is one of the most common causes of disability, especially affecting joints subject to impact loads, such as the knee and hip<sup>(.8)</sup> Thus, knee osteoarthritis (KOA) is a comorbidity that leads to a decrease in body function due to knee joint pain and stiffness, impairing the quality of life of affected individuals.<sup>9</sup>

Thus, ozone therapy has long been used in the treatment of OAJ, in addition to pharmacological and rehabilitation treatments<sup>10</sup>. The positive effects of ozone therapy are provided by the generation of reactive oxygen species (ROS) and lipid oxidative products (LOPs) in the synovial fluid once it has been injected<sup>8</sup>.

Intra-articular injections of ozone inhibit pro-inflammatory cytokines, such as prostaglandin E2, in favor of anti-inflammatory cytokines, such as interleukin 10, transforming growth factor  $\beta$  and interleukin 4, favoring a



reduction in pain and the resorption of edema.<sup>8</sup> In addition to acting on angiogenesis, so that components cooperate to repair the joint, they stimulate fibroblasts, chondrocytes and stem cells.<sup>11</sup> The ozone injections are also effective in reducing pain.

As a result, an increasing number of doctors are using ozone therapy to relieve the symptoms of chronic OAJ, since ozone therapy allows for greater mobility of the joint, pain relief<sup>8</sup> and is a non-operative and less invasive management of patients with this comorbidity<sup>9</sup>. In addition, its intra-articular application is safe and has encouraging short- and medium-term effects on pain control and functional recovery in patients with OAJ.<sup>11</sup>

### **OZONE THERAPY FOR LOW BACK PAIN**

Low back pain (LBP) is a symptom defined as pain between the last ribs and the gluteal area. It is the leading cause of years lived with disability worldwide over the last three decades for both sexes<sup>12</sup>.

Several studies have shown the influence of psychological factors on the development, persistence and treatment of chronic LBP. Coping style, depression, anxiety, catastrophizing and level of pain acceptance are important factors to consider in the overall rehabilitation process of affected patients.<sup>13</sup>

In recent years, lumbar intramuscular-paravertebral injections of an oxygen-ozone mixture (O<sub>2</sub>O<sub>3</sub>) have been proposed in the management of chronic LBP, along with conventional treatments (non-steroidal anti-inflammatory drugs, antidepressants, exercise therapy and psychosocial interventions).<sup>13</sup> Its effectiveness in LBP has been attributed to the modulation of arachidonic acid metabolism, which could explain the anti-inflammatory effect, and to the promotion of local micro-vascularization, reducing ischemia and inflammatory edema in the periradicular area.<sup>13</sup>

After many studies, the researchers observed that the short-calculated oxidative stress achieved by ozone administration can correct a permanent imbalance caused by excessive or chronic oxidative damage. They found that repeated treatment with ozone increases the activity of superoxide dismutase, catalase and glutathione peroxidase, inducing a state of adaptation to oxidative stress with major therapeutic implications<sup>14</sup>.

### **OZONE THERAPY FOR FIBROMYALGIA**

In the foreground, fibromyalgia is a worrying chronic disease that presents itself in a complex way in the form of generalized pain, chronic fatigue, non-restorative sleep, anxiety and depression. Thus, knowing that these symptoms can have a significant impact on the physical and emotional capacities of those affected, there was a need to explore the potential of additional therapies in the management of this disease in order to add to the arsenal of existing treatments.<sup>7</sup>

In this context, studies have shown that ozone therapy is an effective approach in this scenario, due to its ability to exert mild, controlled oxidative stress and modulate the immune system. The result of this ability is shown in the significant 50% improvement in symptoms in 70% of patients, once again highlighting the possibility of considering it as complementary/integrative medicine.<sup>7</sup>

In addition, other research shows that oxygen-ozone autohemotherapy has also proved to be a formidable therapeutic approach for fibromyalgia. The results of this study showed complete rehabilitation of musculoskeletal function and arthralgia after 1 month of follow-up<sup>15</sup>.

## **OZONE THERAPY FOR PLANTAR FASCIITIS, HAMSTRING INJURY, UNILATERAL RADICULAR SYNDROME**

In relation to other applications, medical ozone stands out as a therapeutic element for pathologies such as hypoxia, inflammation and imbalance, with an emphasis on its applications in musculoskeletal injuries. In this context, the results of this treatment have been promising in improving pain intensity, mobility and changes in thermography <sup>16</sup>.

In addition to this scenario, there is also plantar fasciitis and unilateral radicular syndrome. Respectively, in the first case, ozone injection proved to be an effective therapeutic effect, but with a slow onset and longer duration <sup>17</sup>, but the second case brings a conclusion of ozone's therapeutic potential in conditions related to chronic oxidative stress and inflammation, providing symptomatic relief <sup>18</sup>.

Thus, this study is relevant due to the growing prominence of ozone therapy as the main or adjacent treatment in various pathologies with chronic pain complaints, but it still lacks study protocols. This review has limitations due to the lack of homogeneity in the groups of patients analyzed, as well as small samples and a lack of standardization of therapies.

## **CONCLUSION**

Therefore, the studies reviewed have shown a good use of ozone therapy in various treatments for chronic pain, due to its anti-inflammatory effect, thus relieving the symptoms of pain and swelling for various pathologies, especially rheumatological complaints such as knee osteoarthritis, low back pain and fibromyalgia.

We therefore emphasize the need for more studies in order to elucidate and structure protocols that standardize administration routes, therapeutic doses and the most appropriate technique, in order to promote greater safety for professionals and their patients.

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