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Research Article

Various gases for the treatment of neuropathic pain: mechanisms, current status, and future perspectives

Yan Liu[1,#], Tianhao Shen[1,#], Qiuying Li[1], Xue Yu[1], Yu Liu[1], Cheng Zhou[1], Ji Han[2,*], Yongqiang Zhu[1,*]

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Abstract

In recent years, medical gas therapy has emerged as a promising approach for treating neuropathic pain. This review article aimed to investigate the therapeutic effects of medical gas therapy on neuropathic pain and its underlying mechanisms, thereby providing a theoretical foundation for clinical practice. A literature search was conducted using the Web of Science Core Collection database. Co-occurrence analysis of keywords revealed that terms including "neuropathic pain," "nitric oxide," "nitric oxide synthase," "pain," and "ozone" frequently appeared. Cluster analysis grouped these keywords into four primary categories: intervertebral disc disease and gas therapy, mechanisms of neuropathic pain and gas interventions, the role of nitric oxide in modulating neuropathic pain and gas therapy, and the effects of gas therapy on mental disorders in the context of neuropathic pain treatment. The analysis of highly cited literature in the field of medical gas therapy for neuropathic pain emphasizes the crucial roles of nitric oxide and nitric oxide synthase in nerve injury and pain. Various types of gas therapy, including oxygen-ozone therapy and nitric oxide-related therapies, show promise in treating pain following peripheral nerve injury. Oxidative stress and nitric oxide are crucial regulatory factors in the pain signaling associated with trigeminal neuralgia. Ozone therapy alleviates trigeminal pain by inhibiting inflammatory responses, reducing oxidative stress, and modulating neurotransmitter release. Novel nanomaterials, such as manganese oxide nanoparticles, have also demonstrated potential in scavenging free radicals and alleviating sciatic nerve pain. Ozone therapy has shown good clinical efficacy in treating lumbar disc herniation and sciatica, whereas both ozone therapy and hyperbaric oxygen therapy have demonstrated effectiveness and safety in managing postherpetic neuralgia. In conclusion, medical gas therapy for neuropathic pain primarily includes oxygen-ozone therapy, nitric oxide-related therapies, hydrogen sulfide-related therapies, and hyperbaric oxygen therapy. While these therapies exhibit efficacy in managing neuropathic pain, further research is necessary to elucidate their mechanisms of action and safety profiles. Although hyperbaric oxygen therapy and ozone therapy have already been implemented in clinical research, other types of gas therapy are still in the animal testing phase. Therefore, future studies should focus on conducting more multicenter, large-sample randomized controlled trials to accelerate clinical translation and provide more effective treatment options for patients suffering from neuropathic pain.

Key Words: hydrogen sulfide; mechanisms; medical gases; neuralgia; neuropathic pain; nitric oxide; nitric oxide synthase; ozone; therapeutic effects

Introduction

Neuropathic pain typically refers to pain caused by damage to or disease affecting the nervous system.[1] It is a broad term that encompasses various conditions. This type of pain does not result from direct injury to body tissues but instead arises from issues within the nerves themselves, often due to damage, infection, or disease, such as postherpetic neuralgia, pain syndromes, or diabetic peripheral neuropathy.[2,3] Neuralgia is a specific type of neuropathic pain that typically affects a single nerve or a group of nerves. It is characterized by intense or aching pain that occurs along the path or distribution of a peripheral or cranial nerve. This form of neuropathic pain usually arises when a nerve or a group of nerves is damaged, inflamed, or compressed, as observed in conditions such as trigeminal neuralgia and sciatica.[4-6] In the NIH-funded neuralgia research program in the United States, six primary categories receive funding: varicella-zoster virus DNA, oral and facial pain, nervous system disorders, herpes zoster, neuropathic pain, and healthcare. Current research in the United States on neuropathic pain focuses particularly on postherpetic neuralgia and studies related to varicella-zoster virus DNA (**Figure 1**).

As society accelerates and the population ages, the incidence of neuropathic pain has steadily increased, creating a considerable burden on families and the healthcare system. Previous research has focused primarily on traditional treatment methods, such as medications, physical therapy, and acupuncture.[7-10] However, relatively few investigations have investigated the application of medical gas therapy for treating neuropathic pain. While traditional treatments can alleviate symptoms to some extent, their efficacy is often limited, and they may cause adverse effects.[11] In recent years, medical gas therapy has emerged as a promising option for managing neuropathic pain.[12-14]

[1]Department of Intervention, Putuo Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China; [2]Department of Traditional Chinese Medicine Internal Medicine, Putuo Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China
*Correspondence to: Yongqiang Zhu, MD, pt10840@shutcm.edu.cn; Ji Han, doctorhanji@126.com.
https://orcid.org/0009-0001-3983-6791 (Yongqiang Zhu); https://orcid.org/0009-0004-7077-093X (Ji Han)
#Both authors contributed equally to this work.

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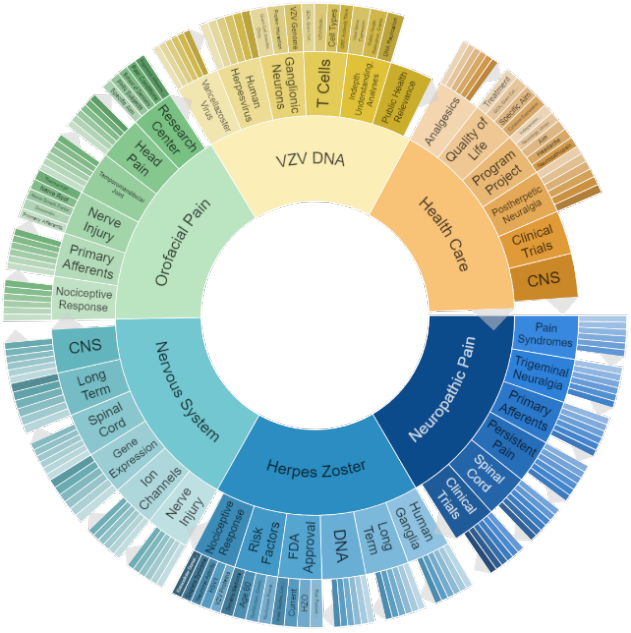

Figure 1 | **Research on neuropathic pain funded by the NIH in the United States (https://reporter.nih.gov/).**
CNS: Central nervous system; VZA: Varicella-Zoster virus.

This article analyzes the key areas of relevant literature regarding medical gas therapy for neuropathic pain identified in the Web of Science Core Collection database and the North American Clinical Trials Registry. The aim of this review article was to explore the therapeutic effects of medical gas therapy on neuropathic pain, as well as the underlying mechanisms involved. Ultimately, the goal is to provide a solid theoretical foundation for clinical practice.

Methods

Data sources

Database

Web of Science Core Collection database.

Retrieval time

December 19, 2024.

Publication date

No restrictions.

Search query

TI=(Neuralgia* OR "Neuropathic Pain*" OR "Neuro* Pain*"OR "Nerve* Pain*" OR Causalgia* OR "Morton Neuroma*" OR "Piriformis Muscle Syndrome" OR "Sciatica*") AND TS=(gas OR Oxygen* OR Hypoxia OR "Nitric Oxide" OR "Carbon Dioxide" OR "Hyperbaric Oxygen*" OR Ozone* OR "Hydro* Peroxide" OR "Nitrous Oxide" OR "Carbon Monoxide" OR "Sulfur Dioxide" OR "Nitrogen Dioxide" OR Hyperoxia OR Argon OR Helium OR "Compressed Air" OR "Pressurized Air" OR Hydrogen OR Oxide OR Hydride OR Nitrogen).

Search results

308 publications.

Data analysis

The literature from the Web of Science Core Collection database was exported as a TXT file containing full records and cited references in plain text format. This file was then imported into VOSviewer version 1.6.19 to create a scientific knowledge map. This map illustrates the development process and structural relationships of scientific knowledge, highlighting the evolution of the subject area. The analysis focuses on the co-occurrence of author keywords, enabling the generation of both keyword visualization maps and density visualization maps. All the metrics were calculated using full counting, which implies that each co-occurrence or cocitation metric has an equal weight. The detailed steps and standard guidelines for operating VOSviewer 1.6.19 are referenced from previous literature,[15] which facilitated the creation of the keyword visualization map. Following this, the main content of highly cited classic literature among the 308 analyzed papers was reviewed, and key research hotspots were summarized.

Analysis of the clinical trial registration protocol

Clinical trial registrations related to gas therapy for neuropathic pain were searched on ClinicalTrials.gov (https://classic.clinicaltrials.gov/), and the key trends among the relevant registered clinical trials were analyzed.

Primary measures

This article primarily investigates the characteristics of keywords associated with gas therapy for neuropathic pain, identifies the hotspots of highly cited literature for various types of pain, and reviews the registration protocols of clinical trials.

Results

Keyword analysis results in the field of gas therapy for neuropathic pain

A frequency analysis of the keywords identified the top 10 keywords as follows: neuropathic pain (58 occurrences), nitric oxide (NO) (46 occurrences), nitric oxide synthase (NOS) (25 occurrences), pain (21 occurrences), ozone (19 occurrences), oxidative stress (16 occurrences), hyperalgesia (14 occurrences), hyperbaric oxygen (14 occurrences), low back pain (14 occurrences), and spinal cord (14 occurrences). A cluster analysis of keywords with a frequency greater than five times identified four distinct clusters: Cluster 1: Chronic pain, epidural gas, herniated disc, low back pain, lumbar disc herniation, nitrous oxide, oxygen-ozone therapy, ozone, ozone therapy, and sciatica. Cluster 2: Hyperalgesia, dorsal root ganglion, hypoalgesia, hyperbaric oxygen, nerve injury, neuropathic pain, NO, rats. Cluster 3: Inducible NOS, inflammation, macrophages, NO, pain, and the spinal cord. Cluster 4: Analgesia, anxiety, cell apoptosis, depression, hydrogen sulfide (H_2S), and oxidative stress. These clusters can be categorized into four primary research directions: (1) Clinical studies focused on intervertebral disc diseases and gas therapy, including epidural gas, nitrous oxide, and ozone. (2) Investigations into the mechanisms underlying neuropathic pain and the effects of gas interventions, such as hyperbaric oxygen, are needed. (3) Research examining the role of NO in the modulation of neuropathic pain, along with studies on gas therapy involving NO and NOS. (4) Research investigating how gas therapy influences mental health conditions in relation to the treatment of neuropathic pain, with a particular focus on H_2S (**Figure 2**).

Hot topics in highly cited literature in the field of gas therapy for neuropathic pain research

The review article presents the key findings from the top 10 most highly cited papers in the field (**Table 1**).[16-25] Meller et al.[16] demonstrated that the sustained production of NO and the subsequent activation of soluble guanylate cyclase in the lumbar spinal cord mediate the hyperalgesia observed in a rat model of neuropathic pain, suggesting a relationship between neuropathic pain and NO. Gao et al.[17] reported that reactive oxygen species (ROS) are involved in the activation of NMDA receptors, a crucial step in central sensitization, thus contributing to the alleviation of neuropathic pain. Sharma et al.[18] identified the antinociceptive properties of resveratrol and curcumin, suggesting that their

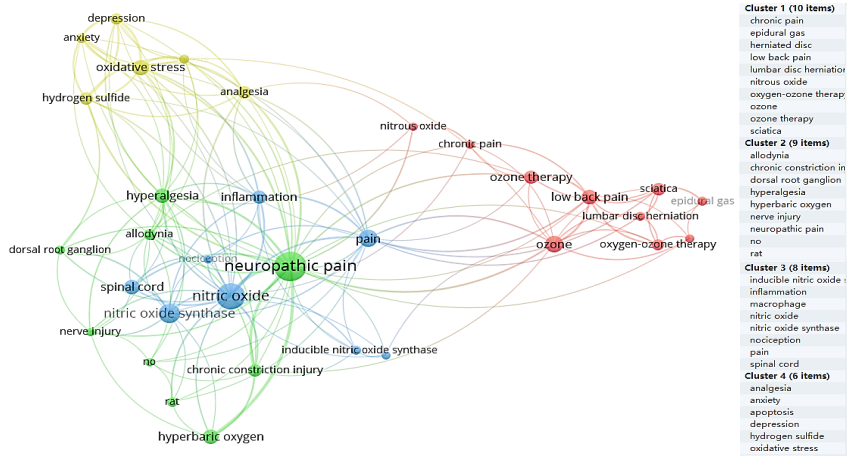

Figure 2 | Visualization and clustering analysis of keywords associated with gas therapy for neuropathic pain (Web of Science Core Collection Database, as of December 19, 2024).
Created using VOSviewer 1.6.19. In the figure, larger nodes represent higher keyword frequencies, whereas thicker lines indicate increased co-occurrence among keywords. Different colors illustrate distinct keyword clusters.

Table 1 | Top 10 highly cited papers related to gas therapy for neuropathic pain in the Web of Science Core Collection Database

Author	Publication year	Gas and factor	Type of neuropathic pain	Title	Study conclusion	Journal	Type of literature	Number of citations
Meller et al.[16]	1992	Nitric oxide	Neuropathic pain	Nitric-oxide mediates the thermal hyperalgesia produced in a model of neuropathic pain in the rat	The development of thermal hyperalgesia in neuropathic pain models may be mediated by the production of nitric oxide and the activation of soluble guanylate cyclase.	*Neuroscience*	Animal study	335
Gao et al.[17]	2007	Reactive oxygen species	Neuropathic pain	Reactive oxygen species are involved in enhancement of NMDA-receptor phosphorylation in animal models of pain	Reactive oxygen species are involved in neuropathic pain and central sensitization, playing a role through the activation of NMDA.	*Pain*	Animal study	207
Sharma et al.[18]	2007	Nitric oxide	Neuropathic pain	Effect of insulin and its combination with resveratrol or curcumin in attenuation of diabetic neuropathic pain: participation of nitric oxide and TNF-alpha	The combined use of insulin and antioxidants, such as resveratrol and curcumin, may alleviate diabetic neuropathic pain, potentially by modulating the levels of nitric oxide and TNF-alpha.	*Phytotherapy Research*	Animal study	154
Lee et al.[19]	2007	Reactive oxygen species	Mechanical neuralgia	The role of reactive oxygen species in capsaicin-induced mechanical hyperalgesia and in the activities of dorsal horn neurons	Reactive oxygen species scavengers can alleviate capsaicin-induced secondary hyperalgesia, indicating that reactive oxygen species play a role in the process of central sensitization.	*Pain*	Animal study	139
Magalhaes et al.[20]	2012	Ozone	Secondary lower back pain	Ozone therapy as a treatment for low back pain secondary to herniated disc: a systematic review and meta-analysis of randomized controlled trials	Oxygen–ozone therapy is effective in treating lower back pain caused by intervertebral disc herniation, demonstrating both short-term and long-term benefits.	*Pain Physician*	Systematic review	107
Gallucci et al.[21]	2007	Oxygen–ozone	Sciatica	Sciatica: treatment with intradiscal and intraforaminal injections of steroid and oxygen–ozone *versus* steroid only	The combination of oxygen–ozone therapy with steroid and local anesthetic injections is more effective in relieving radicular pain caused by acute lumbar disc herniation than steroid and local anesthetic injections alone.	*Radiology*	Randomized controlled trial	105
Kawano et al.[22]	2009	Nitric oxide	Neuropathic pain	Nitric oxide activates ATP-sensitive potassium channels in mammalian sensory neurons: action by direct S-nitrosylation	Nitric oxide activates K-ATP channels in both normal and nerve-injured dorsal root ganglion neurons by directly S-nitrosylating the cysteine residues on the SUR1 subunit.	*Molecular Pain*	Animal study	104
De Alba et al.[23]	2006	Nitric oxide synthase	Neuropathic pain	GW274150, a novel and highly selective inhibitor of the inducible isoform of nitric oxide synthase (iNOS), shows analgesic effects in rat models of inflammatory and neuropathic pain	Inducible nitric oxide synthase plays a role in the development and persistence of pain in inflammatory conditions, and the use of inducible nitric oxide synthase inhibitors can alleviate this pain.	*Pain*	Animal study	104
Muto et al.[24]	2004	Oxygen–ozone	Low back pain or sciatica	Treatment of herniated lumbar disc by intradiscal and intraforaminal oxygen–ozone (O_2–O_3) injection	Oxygen–ozone injection therapy is a safe and effective treatment for low back pain or sciatica resulting from intervertebral disc herniation; however, not all patients show evidence of disc shrinkage.	*Journal of Neuroradiology*	Retrospective case analysis	102
Okubo et al.[25]	2011	Hydrogen sulfide-forming enzyme	Neuropathic pain	Inhibition of t-type calcium channels and hydrogen sulfide-forming enzyme reverses paclitaxel-evoked neuropathic hyperalgesia in rats	Hydrogen sulfide acts via the Ca(v)3.2 T-type calcium channels, and the use of T-type calcium channel blockers or CSE inhibitors can reverse neuropathic pain induced by paclitaxel.	*Neuroscience*	Animal study	92

ATP: Adenosine triphosphatase; CSE: cystathionine-γ-lyase; NMDA: N-methyl D-aspartate; TNF: tumor necrosis factor.

combined use with insulin may help alleviate diabetic neuropathic pain, potentially through the involvement of NO and tumor necrosis factor-alpha. Lee et al.[19] proposed that ROS contribute to central sensitization, at least in part, by sensitizing a wide range of dynamic neurons in the spinal dorsal horn. Magalhaes et al.[20] conducted a systematic review assessing the efficacy of percutaneous ozone injections for treating low back pain secondary to disc herniation. These findings confirmed that this therapy appears to produce positive effects with a low incidence of complications. Gallucci et al.[21] performed a randomized controlled trial comparing the clinical efficacy of epidural and intradiscal injections of steroids, local anesthetics, and a mixture of oxygen and ozone for treating acute radicular pain associated with lumbar disc herniation. They reported that combination treatment provided superior pain relief than injections of steroids and anesthetics alone at the same site after 6 months. Kawano et al.[22] discovered a new mechanism of neuropathic pain, in which NO activates KATP channels in dorsal root ganglion neurons by directly S-nitrosylating cysteine residues in the SUR1 subunit. De Alba et al.[23] demonstrated the role of peripheral blood expression of inducible NOS in pain conditions associated with inflammation, highlighting the potential benefits of using inducible NOS inhibitors in these situations. Muto et al.[24] reported their experience with intradiscal and epidural oxygen–ozone injection therapy in 2200 patients suffering from low back pain or sciatica caused by disc herniation. They reported no adverse reactions during short- or long-term follow-up; among the 1750 patients followed for 6 months, the success rate was 80%, whereas it decreased to 75%, and the failure rate increased to 25% in 1400 patients followed for 18 months. Okubo et al.[25] investigated whether T-type calcium channel blockers and cystathionine γ-lyase, a major H_2S-producing enzyme in peripheral tissues, could reverse paclitaxel-induced neuropathic pain. These results indicated that paclitaxel-induced neuropathic pain may involve increased activity of T-type calcium channels and/or cystathionine γ-lyase in rats.

On the basis of the aforementioned research, gas therapy for neuropathic pain can be summarized as follows:

(1) Oxygen–ozone therapy: This approach treats neuropathic pain, including lower back pain resulting from intervertebral disc herniation, by injecting a mixture of oxygen and ozone. Research indicates that oxygen–ozone therapy can effectively alleviate pain; however, there is insufficient evidence from large-scale randomized controlled trials, and further studies are needed to assess its long-term effectiveness.

(2) NO-related therapies: NO has the ability to activate K-ATP channels and may have beneficial effects on neuropathic pain. Studies have investigated the therapeutic potential of NO donors and scavengers in treating neuropathic pain, but additional research is needed to determine their effectiveness.

(3) H_2S-related therapies: H_2S acts as a gaseous neurotransmitter that can activate T-type calcium channels and plays a role in the development of neuropathic pain. Research indicates that drugs that inhibit T-type calcium channels and reduce H_2S production can help alleviate neuropathic pain, suggesting that these agents may have therapeutic potential.

(4) Hyperbaric oxygen therapy: Some studies have explored the effectiveness of hyperbaric oxygen therapy for neuropathic pain, resulting in pain relief in certain patients; however, further research is needed to verify its efficacy.

In conclusion, gas therapy has promising potential for treating neuropathic pain but remains in the early stages of investigation. Additional high-quality studies are needed to determine their efficacy and safety.

Gas therapy for neuropathic pain

NO, ROS, inflammatory cytokines, and various signaling pathways (including the Nrf2/HO-1 pathway) play vital roles in neuropathic pain.[16, 18, 26-29] NO, which is produced by different isoforms of NOS (neuronal NOS, endothelial NOS, inducible NOS), has been implicated in the development of neuropathic pain through its effects on spinal cord mechanisms and peripheral inflammation.[26,30-32] Research has shown that inhibiting the production of NO or using NO scavengers can help reduce pain symptoms in animal models.[26,30,31,33] Furthermore, some studies suggest that nitrogen oxides may influence the expression of opioid receptors, potentially affecting the effectiveness of opioid-based pain therapies.[34] ROS, hydrogen peroxide, and other oxidants, such as 4-hydroxy-2-nonenal, have also been linked to neuropathic pain.[35] Antioxidants such as N-acetylcysteine (NAC) and hydrogen-rich saline may effectively reduce hyperalgesia by scavenging ROS and mitigating oxidative stress.[36,37]

Various therapeutic strategies targeting these pathways and molecules have been investigated. For example, H_2S donors (such as NaHS and DADS) and inducers of heme oxygenase-1 (such as cobalt protoporphyrin IX) have shown analgesic effects in neuropathic pain models, likely through a reduction in oxidative stress and inflammatory responses. Additionally, hyperbaric oxygen therapy has been explored for its potential to alleviate neuropathic pain. Research suggests that hyperbaric oxygen therapy can provide both immediate and long-lasting analgesic effects by modulating inflammatory responses, oxidative stress, and autophagy in the spinal cord and dorsal root ganglia.[39-45]

Gas therapy for pain following peripheral nerve injury

The literature mainly emphasizes the mechanisms and treatment approaches for pain resulting from peripheral nerve injury. NO and NOS are crucial in the processes associated with nerve injury and pain. Research indicates that the expression and activity of various NOS isoforms (including inducible NOS [iNOS], neuronal NOS [nNOS], and endothelial NOS [eNOS]) are closely linked to the initiation and progression of pain after nerve injury.[46-49] Furthermore, NO donor drugs and NOS inhibitors have demonstrated some promise in the management of neuropathic pain; however, additional studies are needed to elucidate their specific mechanisms of action and clinical efficacy.[50]

The main findings related to gas therapy for pain resulting from peripheral nerve injury encompass several key points. First, research indicates that NO donor drugs can suppress the expression and activity of iNOS in models of nerve injury, which in turn reduces neuroinflammation and pain sensitivity.[46, 51] Second, NOS inhibitors (such as l-NAME) have proven effective in alleviating pain symptoms associated with nerve injury, including mechanical allodynia and thermal hyperalgesia.[47,49,50] Furthermore, treatment with an oxygen–nitrogen mixture has been shown to have analgesic effects on neuropathic pain, possibly through NMDA receptor blockade.[52] These discoveries offer a theoretical framework and practical support for the use of gas therapy in managing pain following peripheral nerve injury.

Gas therapy for trigeminal neuralgia

Trigeminal neuralgia is a chronic pain characterized by a complex underlying mechanism that involves various neurotransmitters and signaling pathways. Research has highlighted several key points. First, satellite glial cells within the trigeminal ganglion are crucial for the transmission and maintenance of pain.[53] Second, oxidative stress and NO are significant regulatory factors in the pain signaling processes associated with trigeminal neuralgia.[53,54] Finally, inflammatory factors and oxidative stress play a role in the onset and persistence of pain by activating relevant signaling pathways, including the NMDA/NO pathway and MAPKs.[54]

Recent research findings on gas therapy for trigeminal neuralgia reveal several important aspects. First, a previous study has shown that local injections of ozone can provide substantial therapeutic benefits in alleviating pain symptoms.[55] Second, ozone alleviates pain by inhibiting inflammatory responses, reducing oxidative stress, and modulating the release of neurotransmitters.[55] Third, ozone therapy has the potential to promote nerve regeneration and repair, leading to an improvement in pain symptoms.[55] Finally, ozone therapy is recognized for its high safety profile and minimal side effects.

Gas therapy for sciatica

Innovative nanomaterials, especially manganese oxide nanoparticles, have shown considerable potential in removing ROS and relieving symptoms of sciatica.[56] Additionally, ozone therapy, a cutting-edge treatment approach, has yielded positive clinical outcomes in the treatment of lumbar disc herniation and sciatica.[57-60] The key findings related to ozone therapy include the following: first, ozone therapy effectively reduces pain in patients suffering from lumbar disc herniation and sciatica, leading to increased quality of life. Second, ozone therapy alleviates pain by lowering oxidative stress, suppressing inflammatory responses, and modulating the release of neurotransmitters. Third, ozone therapy is recognized for being minimally invasive, having a high safety profile, and exhibiting few adverse effects. Fourth, ozone therapy has analgesic effects through downregulating the expression of P2X3 and P2X7 purinergic receptors in the dorsal root ganglia.[58]

In conclusion, oxidative stress and NO are critical factors in the occurrence and development of nerve injury and pain. Ozone therapy has exhibited promising clinical effectiveness in treating conditions such as lumbar disc herniation and sciatica. Moreover, novel nanomaterials such as manganese oxide nanoparticles have great potential for scavenging ROS and alleviating neuropathic pain. Future research should aim to clarify the specific mechanisms of action and long-term efficacy of ozone therapy while refining treatment strategies. Additionally, further investigations of the role of novel nanomaterials in the treatment of neuropathic pain are essential.

Gas therapy for postherpetic neuralgia

Postherpetic neuralgia presents considerable treatment challenges and is often associated with unsatisfactory therapeutic outcomes. Both oxidative stress and NO are key contributors to the development and progression of postherpetic neuralgia. As a novel treatment approach, ozone therapy has demonstrated encouraging clinical results in the management of this condition.[61]

Ozone therapy has proven to be effective and safe for treating postherpetic neuralgia, whether administered alone or in conjunction with other treatment options such as medications, hyperbaric oxygen therapy, and pulsed radiofrequency.[61] Research indicates that the combination of ozone autohemotherapy and medication is more effective in reducing postherpetic neuralgia symptoms than medication alone.[61] Additionally, ultrasound-guided ozone injections into the cervical dorsal root ganglia have shown efficacy in alleviating herpes-related pain, particularly in patients with a shorter duration of symptoms.[62] The use of pulsed radiofrequency in conjunction with ozone therapy may offer improved outcomes for treating postherpetic neuralgia compared with ozone therapy used in isolation.[63] Furthermore, a previous study suggested that hyperbaric oxygen therapy can significantly improve treatment outcomes for postherpetic neuralgia by relieving pain, accelerating the healing of vesicles and skin lesions, lowering the occurrence of postherpetic neuralgia, and enhancing the overall mental well-being of patients.[64] Future investigations should delve deeper into the specific mechanisms behind ozone therapy and its long-term effectiveness while refining treatment protocols. Moreover, further attention should be given to the role of hyperbaric oxygen therapy in the management of postherpetic neuralgia.

Analysis of Clinical Trial Registration Protocols

Currently, there are 10 clinical trial protocols investigating gas therapy for neuropathic pain registered at ClinicalTrials.gov, all of which are categorized as interventional studies (**Table 2**). The latest active trial currently recruiting participants, initiated in 2023, is titled "The effects of ultrasound-guided ozone and lidocaine injections in piriformis syndrome." This trial focuses on sciatica (NCT06130618). In 2022, a study titled "Nitrous oxide as a treatment for fibromyalgia" focused on central neuropathic pain (NCT05357066), suggesting an increasing interest in neuropathic pain related to muscle conditions in recent research. Furthermore, a 2020 trial named "Ozone therapy for chemotherapy-induced peripheral neuropathy: RCT (O3NPIQ)" primarily targets neuropathic pain and pain syndromes (NCT04299893), and the outcomes of this study are highly anticipated.

Table 2 | **Clinical interventional research protocols for gas therapy for neuropathic pain registered at ClinicalTrial.gov**

NCT number	Study title	Study status	Condition	Intervention	First posted
NCT06130618	The effects of ultrasound guided ozone and lidocaine injections in piriformis syndrome	Recruiting	Piriformis; syndrome	Other: Ozone Drug: Lidocain	November 14, 2023
NCT05357066	Nitrous oxide as treatment for fibromyalgia	Recruiting	Fibromyalgia; central neuropathic pain	Drug: Nitrous oxide gas for inhalation Drug: Placebo	May 2, 2022
NCT04299893	Ozone therapy in chemotherapy-induced peripheral neuropathy: RCT (O3NPIQ)	Recruiting	Chemotherapy-induced peripheral neuropathy; pain, neuropathic; pain syndrome	Drug: Ozone Drug: Oxygen	March 9, 2020
NCT03354806	Peripheral analgesia in painful diabetic neuropathy	Withdrawn	Diabetic neuropathy peripheral; neuropathic pain; diabetic foot infection	Procedure: Continuous peripheral nerve blocks Procedure: Analgesic treatment	November 28, 2017
NCT02957851	EMONO for the treatment of peripheral neuropathic pain (ProtoTOP)	Completed	Neuralgia	Drug: Medical air Drug: EMONO	November 8, 2015
NCT02473016	Nasal carbon dioxide for the symptomatic treatment of classical trigeminal neuralgia	Completed	Trigeminal neuralgia	Drug: Carbon dioxide drug delivery system	June 16, 2015
NCT02246517	The effect of N_2O on chronic neuropathic pain patients	Unknown	Neuropathic pain	Drug: N_2O Drug: Oxygen	September 22, 2014
NCT01633086	A study on the safety and efficacy of nitric oxide gel in subjects with painful diabetic neuropathy	Completed	Neuropathic pain	Drug: Nitric oxide gel Drug: Placebo gel	July 4, 2017
NCT01172600	Effect of nitrous oxide in treating neuropathic pain: a study in chronic low back pain patients	Completed	Low back pain; radiating pain	Other: Entonox Other: Oxygen	July 30, 2010
NCT00866424	Clinical trial of hyperbaric oxygen treatment in trigeminal neuralgia patients	Unknown	Trigeminal neuralgia; pain	Procedure: Hyperbaric oxygen, Mock hyperbaric chamber	March 20, 2009

EMONO: Equimolar mixture of oxygen and nitrous oxide; RCT: randomized controlled trial.

Limitations

The article included only one literature source from the Web of Science Core Collection database, which may have led to omissions of relevant information from other databases. However, the Web of Science Core Collection provides highly cited data that facilitate the analysis of research hotspots. Therefore, the identified literature hotspots in the article are somewhat representative. Future research will continue to expand the scope of literature database searches. While this review explores the potential of various gas therapies for neuropathic pain, it does not address key factors such as administration routes (e.g., direct administration *versus* gas molecule donors), dosage, and frequency of administration. This omission is due to the fact that most studies are still in the animal experimentation phase or in the early stages of clinical research with small sample sizes, which leads to significant variability in some administration methods. The focus of this article is primarily on the recent findings related to efficacy and safety. Future studies will provide a more detailed discussion on these critical issues.

Discussion

Result analysis

This article provides an in-depth analysis of medical gas therapy for neuropathic pain, addressing various aspects, such as data sources, search methods, data analysis, clinical trial protocols, and primary outcome measures. By conducting keyword co-occurrence and clustering analyses on 308 articles related to neuropathic pain obtained from the Web of Science Core Collection database, this study identified significant areas of interest in the field of medical gas therapy for neuropathic pain. These areas primarily include clinical application studies of gas therapy for intervertebral disc disorders, investigations into the mechanisms of neuropathic pain and gas interventions, studies on the role of NO in modulating neuropathic pain and gas therapy, and investigations into the effects of gas therapy on mental health in the treatment of neuropathic pain.

The literature review on the mechanisms of gas therapies for neuropathic pain indicates that nitric oxide activates K-ATP channels, which contributes to pain relief. Furthermore, nitric oxide donor drugs and nitric oxide synthase inhibitors have been found to alleviate neuropathic pain symptoms. Antioxidants such as N-acetylcysteine can also scavenge reactive oxygen species,[65] further aiding in the relief of neuropathic pain.

The literature review emphasizes that NO and H_2S play significant roles in the development and progression of neuropathic pain within various gas therapies. The sustained production of nitric oxide and the activation of soluble guanylate cyclase mediate hyperalgesia in rat models of neuropathic pain. iNOS is involved in the processes of nerve injury and pain, and iNOS inhibitors have been shown to alleviate pain. H_2S activates T-type calcium channels, contributing to the onset and progression of neuropathic pain. Additionally, drugs that inhibit T-type calcium channels and the production of H_2S can effectively reduce neuropathic pain. Furthermore, the exogenous administration of nitric oxide donor drugs, nitric oxide synthase inhibitors, and H_2S donor drugs can modulate the levels of endogenous gas molecules, resulting in analgesic effects. Exogenous gases such as oxygen and ozone can also impact pain; for example, hyperbaric oxygen therapy and ozone therapy have been studied for their potential to relieve neuropathic pain. Future research is necessary to further explore the mechanisms by which these endogenous and exogenous gas molecules regulate pain, providing a theoretical foundation for the development of new pain treatment methods.

This article also explores the prominent research hotspots in the field of medical gas therapy for neuropathic pain, summarizing the primary types of gas therapy, which include oxygen–ozone therapy, NO-related therapy, H_2S-related therapy, and hyperbaric oxygen therapy. Each therapy is evaluated in terms of its current research status and potential applications. Moreover, this article offers an in-depth analysis of gas therapy for different types of neuropathic pain, such as pain resulting from peripheral nerve injury, trigeminal neuralgia, sciatica, and postherpetic neuralgia, highlighting the key research outcomes and treatment approaches for each type of pain. Regarding clinical trials, the article reviews 10 interventional research protocols related to neuropathic pain registered with ClinicalTrial.gov, with the most recent studies focusing on neuropathic pain affecting the muscles.

Overall, gas molecules play a significant role in the development and progression of neuropathic pain. Further research on their mechanisms of action and the development of new gas therapies holds great potential. Although gas therapies such as hyperbaric oxygen and ozone therapies have been utilized in some clinical studies, more high-quality research is necessary to validate their efficacy and safety. In the future, attention should be focused on the application of innovative gas therapies and nanomaterials in pain treatment, providing new strategies for pain management.

Summary of gas therapy for neuropathic pain

Gas therapy for neuropathic pain has several key characteristics: Variety: It includes multiple treatment approaches that can be tailored to the patient's specific condition and constitution.[66] Notable efficacy: These therapies have demonstrated significant pain relief for a range of neuropathic pain disorders. Relatively high safety: Most of these treatments are considered safe when they are administered under appropriate supervision and monitoring. Limited clinical research: The majority of studies conducted thus far are based on animal models, and further clinical trials are necessary. Importantly, all therapies should be administered under the supervision of a qualified healthcare professional, considering individual differences and potential side effects to ensure both effectiveness and safety. According to the literature review, **Table 3** outlines eight types of gas therapy for neuropathic pain: NO-related therapy, ROS scavenging therapy, hyperbaric oxygen therapy, ozone therapy, novel nanomaterial therapy, H_2S and antioxidant stress-related therapy, H_2S donor drug therapy, and hydrogen-rich saline therapy. Among these, only hyperbaric oxygen therapy and ozone therapy have been utilized in clinical research, while the remaining types of gas therapy are still in the animal testing phase.

Conclusions and prospects

Taken together, gas therapy has potential application value in the treatment of neuropathic pain, but it is still in the exploratory stage, and more high-quality research is needed to clarify its efficacy and safety. Future researchers could consider the following aspects:

(1) Conducting more large-scale, multicenter randomized controlled trials to validate the efficacy and safety of gas therapy in the treatment of neuropathic pain.

(2) The specific mechanisms of action of gas therapy should be further investigated to provide a theoretical basis for its clinical application.

(3) Investigating the application value of different types of gas therapy in the treatment of various types of neuropathic pain to provide personalized treatment plans for patients.

(4) Investigating the efficacy of combining gas therapy with other treatment methods to enhance therapeutic outcomes.

(5) Focusing on the application of novel gas therapy and nanomaterials in the treatment of neuropathic pain to provide new ideas and methods for managing this condition.

Table 3 | **Summary of the mechanisms, efficacy, and safety of gas therapy for treating neuropathic pain**

Gas therapy	Drugs and measures	Mechanism of action	Therapeutic effects	Safety	Current research stage
Nitric oxide-related therapy[16,18,22]	Nitric oxide donor drugs, nitric oxide synthase inhibitors	Regulating pain signal transmission by affecting spinal mechanisms and peripheral inflammation	Alleviating symptoms of neuropathic pain, regulating the expression of opioid receptors, and influencing the effectiveness of pain treatment	Paying attention to the dosage and duration of use of nitric oxide donor drugs, as overdose may lead to side effects	Animal study
Reactive oxygen species scavenging therapy[17,19]	Antioxidants such as N-acetylcysteine	Reducing hyperalgesia by scavenging reactive oxygen species and alleviating oxidative stress	Effectively alleviating neuropathic pain	Antioxidants are generally considered to have a high safety profile, but individual differences and potential side effects should still be taken into account	Animal study
Hyperbaric oxygen therapy[39-45,61]	Improving tissue oxygenation by increasing blood oxygen levels and oxygen partial pressure	Regulating the inflammatory response, oxidative stress, and autophagy in the spinal cord and dorsal root ganglia	Producing both acute and long-term analgesic effects	Antioxidants are generally considered to be safe, but individual differences and potential side effects should still be taken into account	Animal study, clinical trial
Ozone therapy[20,21,24]	Ozone injections and ozone autohemotherapy	Alleviating pain by inhibiting the inflammatory response, reducing oxidative stress, and regulating neurotransmitter release	Effective for various types of neuropathic pain, such as trigeminal neuralgia, sciatica, and postherpetic neuralgia	It should be conducted in specialized institutions, with attention to the risks of oxygen toxicity and other hazards	Animal study, clinical trial
Novel nanomaterial therapy[56]	Manganese oxide nanoparticles	Scavenging reactive oxygen species to alleviate neuropathic pain	Exhibiting potential in scavenging free radicals and alleviating pain	Further research is needed on its biocompatibility and long-term side effects	Animal study
Antioxidant stress-related therapy[29,38]	Antioxidants include cobalt protoporphyrin IX, which exerts its effects by enhancing the production of endogenous hydrogen sulfide	Reducing neuropathic pain by activating antioxidant responses and inhibiting oxidative stress	Exhibiting efficacy for conditions such as neuropathic pain resulting from chemotherapy	It should be conducted in specialized institutions, paying attention to dosage and duration of use, as excessive amounts may lead to side effects	Animal study
Hydrogen sulfide donor drug therapy[29,38]	GYY4137 and similar drugs can gradually release hydrogen sulfide	They work through mechanisms such as regulating neurotransmitter release, inhibiting inflammatory responses, and reducing oxidative stress	They provide notable relief for various forms of neuropathic pain, including pain caused by chemotherapy, chronic osteoarthritis, and diabetic neuropathy	They have relatively high safety and minimal side effects, but individual differences and potential side effects should still be taken into consideration	Animal study
Hydrogen-rich saline therapy[36,37]	Intraperitoneal or intrathecal injection of hydrogen-rich saline	Hydrogen-rich saline, as an antioxidant, can reduce oxidative stress, inhibit inflammatory responses, and regulate the release of neurotransmitters	Hydrogen-rich saline effectively alleviates neuropathic pain, chronic osteoarthritis pain, and diabetic neuropathic pain	High safety and minimal adverse reactions	Animal study

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