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# Mesenchymal stem cells as a therapeutic strategy to combat oxidative stress-mediated neuropathic pain

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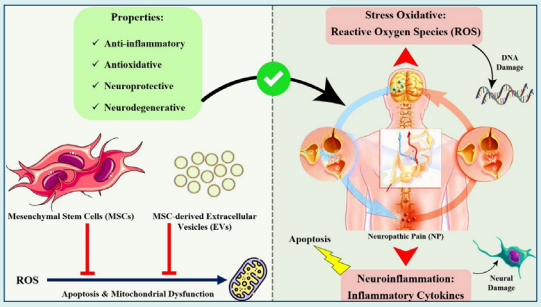
**Abstract**




Neuropathic pain, a chronic condition resulting from somatosensory system damage, remains a significant clinical challenge due to its complex pathophysiology and inadequate response to traditional therapies. Oxidative stress, characterized by an imbalance between free radicals production and antioxidant defenses, plays a pivotal role in the development and maintenance of neuropathic pain. Mesenchymal stem cells (MSCs) are multipotent stromal cells with the ability to differentiate into various cell types and possess immunomodulatory, anti-inflammatory, and regenerative properties, making them promising candidates for novel pain management strategies. Preclinical studies demonstrate that MSCs can reduce inflammation, scavenge reactive oxygen species (ROS), promote nerve regeneration, and modulate pain signaling pathways. Various administration routes, including intravenous and intrathecal, have been investigated to optimize MSC delivery and efficacy. Additionally, MSC-derived extracellular vesicles (EVs) represent a cell-free alternative with substantial therapeutic potential. Despite encouraging preclinical findings, further research is needed to refine MSC-based therapies, including the exploration of combination treatments and rigorous clinical trials, to translate these promising results into effective clinical applications for neuropathic pain relief. This review explores the therapeutic potential of MSCs in alleviating oxidative stress-mediated neuropathic pain.

## Introduction

Neuropathic pain is a chronic pain disorder that persists beyond the normal healing process, affecting millions of individuals worldwide.[1] This type of pain is characterized by persistent discomfort resulting from damage or dysfunction within the somatosensory system, which processes sensory information from the peripheral to the central nervous system.[2] The somatosensory system encompasses neural pathways that, when compromised, can lead to a range of painful sensations that extend beyond the typical nociceptive pain response.[3] These sensations may include shooting, burning, or electric shock-like pain, as well as allodynia and hyperalgesia, which refer to pain from non-painful stimuli and increased sensitivity to pain, respectively.[3]

Neuropathic pain manifests in various forms, including burning sensations, sharp shooting pains, and the experience of pain from stimuli that would not normally be painful.[2] The causes of neuropathic pain are diverse and can include nerve damage from injuries, diabetes, autoimmune diseases, or infections.[4] Damage to the brain or spinal cord, such as from a stroke or trauma, can also trigger neuropathic pain.[5] Although the exact mechanisms are still being elucidated, it is thought to involve a combination of hyperexcitable nerves, disrupted communication between nerves, and changes in the brain's processing of pain signals.[6]

The mechanisms underlying neuropathic pain involve both peripheral and central components.[7] Peripherally, damaged nerve fibers can become hyperexcitable,

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leading to spontaneous pain and heightened sensitivity (hyperalgesia) due to alterations in ion channels and inflammatory processes driven by immune cells releasing pro-inflammatory cytokines.[8] Centrally, nerve injury can result in maladaptive plasticity in the spinal cord and brain, increasing excitability in the dorsal horn and disrupting pain modulation pathways, which amplifies pain responses.[9-11]

Mesenchymal stem cells (MSCs) offer promising therapeutic potential for neuropathic pain through their anti-inflammatory, immunomodulatory, and regenerative properties.[12] MSCs can target both peripheral and central mechanisms of neuropathic pain by reducing inflammation, modulating immune responses, and promoting nerve repair and regeneration.[13] These unique capabilities position MSCs as a novel approach for addressing the complex pathophysiology of neuropathic pain.[13]

### *The role of oxidative stress in neuropathic pain development*

Oxidative stress plays a pivotal role in the pathogenesis of neuropathic pain, which is characterized by an imbalance between the production of oxidants, such as reactive oxygen species (ROS), and the body's antioxidant defenses.[14] ROS, including superoxide anions (O2•−), hydroxyl radicals (•OH), and hydrogen peroxide (H2O2), are among the most common free radicals.[14] When the generation of these reactive molecules exceeds the neutralizing capacity of antioxidants, oxidative stress ensues, leading to cellular damage.[14] In neuropathic pain, oxidative stress contributes to neuronal injury and inflammation, resulting in alterations to pain signaling pathways.[15]

The detrimental effects of oxidative stress on cellular and neuronal structures are substantial.[15] ROS can damage essential cellular components, such as lipids, proteins, and DNA, ultimately leading to dysfunction and apoptosis.[16] In neurons, oxidative stress impairs mitochondrial function, disrupts cellular metabolism, and triggers apoptotic pathways, culminating in the loss of neuronal integrity and function.[17] This neuronal damage exacerbates the dysregulation of pain signaling mechanisms, perpetuating the chronic pain cycle.[18] Therefore, targeting oxidative stress and mitigating its harmful effects on cells and neurons is crucial for the development of effective therapeutic strategies for neuropathic pain.[14]

### *Mesenchymal stem cells: A therapeutic strategy*

Despite extensive research, current treatments for neuropathic pain are inadequate. Medications such as opioids, anticonvulsants, and antidepressants often provide limited efficacy and are associated with side effects.[19] Furthermore, these treatments primarily focus on symptom management rather than addressing the underlying causes of neuropathic pain, underscoring the need for innovative therapeutic approaches to meet this critical unmet medical need.[19]

MSCs have emerged as a promising therapeutic approach for combating oxidative stress-mediated neuropathic pain.[20] MSCs are multipotent stromal cells capable of differentiating into various cell types, including osteocytes, chondrocytes, and adipocytes.[21] They possess unique immunomodulatory, anti-inflammatory, and regenerative properties, making them ideal candidates for treating neuropathic pain.[22]

MSCs secrete a variety of bioactive molecules, including anti-inflammatory cytokines, growth factors, and antioxidants, which can mitigate oxidative stress and promote neuronal survival and repair.[23] These cells can home to sites of injury and inflammation, modulating the local immune response and facilitating tissue regeneration.[24] Moreover, MSCs have been shown to enhance neurogenesis and synaptic plasticity, both of which are critical for restoring normal sensory function in neuropathic pain conditions.[24]

Preclinical studies have demonstrated the efficacy of MSCs in reducing pain behaviors and inflammation in various models of neuropathic pain.[25] However, the precise mechanisms by which MSCs exert their therapeutic effects remain incompletely understood, warranting further research to optimize their clinical application.[25]

## Mechanisms of oxidative stress-induced neuropathic pain

### *Pathophysiology*

The pathophysiological mechanisms through which oxidative stress induces neuropathic pain include the following (Fig. 1):

*A. Mitochondrial Dysfunction*: Mitochondria serve as both a source and target of ROS.[26] Oxidative stress can impair mitochondrial function, leading to reduced ATP production and increased ROS generation.[27] This dysfunction is particularly critical in neurons due to their high energy demands. Impaired mitochondrial function results in a bioenergetic deficit, contributing to neuronal damage and cell death.[28] Furthermore, increased ROS production from dysfunctional mitochondria exacerbates oxidative stress, creating a vicious cycle of cellular damage.[29] Mitochondrial impairment also triggers apoptotic pathways via the release of cytochrome c and the activation of caspases, further contributing to neuronal loss and the chronicity of pain.[30]

The detrimental effects of oxidative stress on cellular and neuronal structures are profound. ROS can damage critical cellular components, including lipids, proteins, and DNA, leading to cellular dysfunction and apoptosis.[31] In neurons, oxidative stress impairs mitochondrial function, disrupts cellular metabolism, and activates

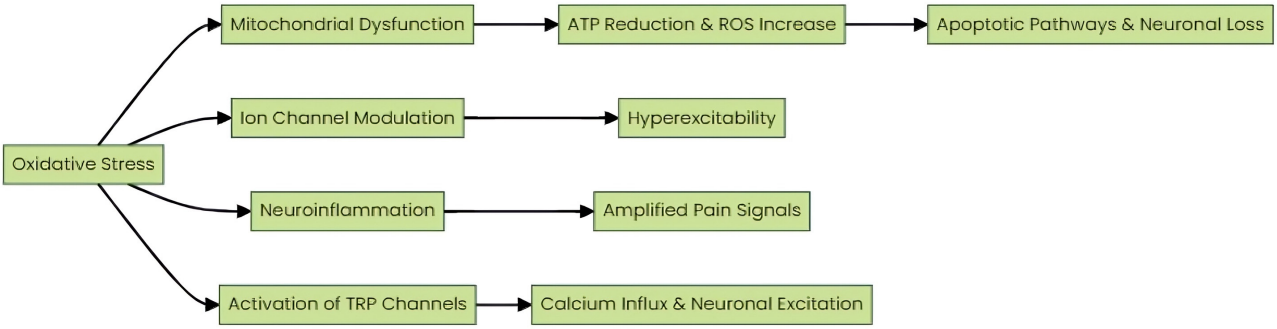


**Fig. 1.** Mechanisms by which oxidative stress induces neuropathic pain. Pathophysiological mechanisms through which oxidative stress induces neuropathic pain, including mitochondrial dysfunction, ion channel modulation, neuroinflammation, and activation of TRP channels.

apoptotic pathways, ultimately resulting in the loss of neuronal integrity and function.[32] This neuronal damage exacerbates dysregulation in pain signaling mechanisms, perpetuating the chronic pain cycle.[33] Therefore, targeting oxidative stress and mitigating its harmful effects on cells and neurons is essential for developing effective therapeutic strategies for neuropathic pain.[34]

*B. Ion channel modulation*: Oxidative stress can modulate the function of various ion channels, including voltage-gated sodium (Nav) and calcium (Cav) channels.[35] ROS can enhance Nav channel activity, particularly by oxidizing critical thiol groups on channel proteins, leading to the hyperexcitability of nociceptive neurons.[36] This hyperexcitability results in increased spontaneous neuronal firing and heightened pain signaling.[36] Similarly, oxidative stress can alter Cav channel function, disrupting intracellular calcium homeostasis.[37] Elevated intracellular calcium levels activate signaling cascades, including those involving protein kinases and phosphatases, which further modulate pain signaling pathways and contribute to synaptic plasticity changes that underlie chronic pain states.[38]

*C. Neuroinflammation*: Oxidative stress activates glial cells, including microglia and astrocytes.39 This activation results in the release of various inflammatory mediators, including cytokines, chemokines, and ROS.[40] These mediators play a crucial role in modulating neuronal excitability and synaptic transmission.[40] Specifically, they lower the activation threshold of nociceptive neurons, thereby amplifying pain signals.[41] The persistent presence of these inflammatory mediators can sustain a state of chronic neuroinflammation, which contributes to the maintenance and exacerbation of neuropathic pain.[42]

*D. Activation of TRP channels:* Transient receptor potential (TRP) channels, particularly TRPA1 and TRPV1, play a crucial role in the sensory perception of pain and are highly sensitive to oxidative stress.[43] ROS, a byproduct of mitochondrial dysfunction, can activate these TRP channels.[44] Upon activation, TRPA1 and TRPV1 facilitate the influx of calcium ions ($Ca^{2+}$) into neurons.[44] This calcium influx is a pivotal event, leading to enhanced neuronal excitability and the propagation of nociceptive signals.[45] Consequently, this cascade of events contributes to the development and maintenance of neuropathic pain.[45]

Emerging research elucidates the intricate role of ROS in neuronal damage and pain signaling cascades.[46] ROS-mediated oxidative stress is implicated in neurodegenerative disorders and chronic pain conditions, highlighting the importance of targeting ROS pathways for therapeutic interventions.[47] The pathophysiological mechanisms through which oxidative stress induces neuropathic pain include the activation of TRP channels, particularly TRPA1 and TRPV1, which are sensitive to oxidative stress.[48] ROS can activate these channels, resulting in calcium influx, subsequent neuronal excitation, and pain.[48] Understanding the complex interplay between ROS and neuronal function offers valuable insights into novel treatment strategies aimed at mitigating neurodegeneration and pain perception.

## *How molecules involved in oxidative stress induce neuropathic pain (mechanism of their action)*

Key molecules involved in oxidative stress that induce neuropathic pain include:

*A. Superoxide anion (O2•−):* A primary ROS, superoxide anion is produced through the partial reduction of molecular oxygen in mitochondria.[49] This anion can react with nitric oxide (NO) to form peroxynitrite (ONOO−), a highly reactive nitrogen species.[49] Peroxynitrite exerts deleterious effects by nitrating tyrosine residues in proteins, oxidizing lipids, and inducing DNA strand breaks.[50] These modifications disrupt cellular homeostasis and activate various protein kinases and transcription factors, including nuclear factor-kappa B (NF-κB), leading to the upregulation of pro-inflammatory cytokines and mediators, which enhance pain signaling pathways.[51]

*B. Hydroxyl radical (•OH)*: Generated via the Fenton reaction, where H2O2 reacts with transition metal ions, the hydroxyl radical is among the most reactive ROS.[52] Due to its high reactivity, •OH initiates lipid peroxidation, leading to the formation of malondialdehyde and

4-hydroxynonenal.[53] These lipid peroxidation products induce structural and functional changes in cell membranes, contributing to neuronal damage.[54] In addition, •OH oxidizes and fragments proteins and DNA, impairing neuronal integrity and function, thereby exacerbating pain sensation.[54]

*C. Hydrogen peroxide (H2O2)*: As a relatively stable ROS, hydrogen peroxide can permeate cellular membranes and act as a signaling molecule.[55] Within neurons, H2O2 modulates redox-sensitive signaling pathways, such as the mitogen-activated protein kinase (MAPK) pathway, which includes extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK.[56] The activation of these kinases leads to the phosphorylation of transcription factors and the expression of genes involved in inflammation and apoptosis, contributing to the development of neuropathic pain.[56]

*D. 4-Hydroxynonenal (4-HNE):* A toxic aldehyde produced during lipid peroxidation, 4-HNE forms covalent adducts with nucleophilic amino acid residues in proteins, resulting in the formation of advanced lipoxidation end products (ALEs).[57] These adducts alter protein structure and function, impairing cellular processes.[58] Notably, 4-HNE can activate transient receptor potential ankyrin 1 (TRPA1) channels, which are expressed in sensory neurons.[58] TRPA1 activation by 4-HNE induces calcium influx, increasing neuronal excitability and pain perception.[59] This mechanism underscores the pivotal role of lipid peroxidation products in modulating pain pathways (Fig. 2).[59]

## Traditional therapies for the alleviation of neuropathic pain

Neuropathic pain, a complex and chronic condition arising from nervous system damage, poses significant therapeutic challenges.[60] Traditional therapies aim to alleviate pain by targeting various pathophysiological mechanisms, but their efficacy often varies among individuals.[61] Moreover, these therapies do not directly address oxidative stress, a key underlying mechanism in neuropathic pain, which necessitates the exploration of novel treatments such as MSCs.[60] Below, we explore the primary traditional therapies used in clinical practice for managing neuropathic pain.[62]

### *Pharmacological therapies*

*A. Antidepressants*: Tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, are commonly prescribed for neuropathic pain.[63] These drugs inhibit the reuptake of norepinephrine and serotonin, increasing their availability in the synaptic cleft. This is believed to enhance descending inhibitory pathways, reducing pain perception.[64] Selective serotonin and norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, offer a better side-effect profile compared to TCAs.[64] While these medications modulate neurotransmitter levels, they do not directly address oxidative stress, though they may indirectly affect oxidative pathways by altering neuronal activity and inflammation.[65]

*B. Anticonvulsants*: Medications like gabapentin and pregabalin are widely used due to their efficacy in reducing neuropathic pain.[66] These drugs bind to the α2δ subunit of voltage-gated calcium channels in the central nervous system, reducing calcium influx into nerve terminals and thereby diminishing the release of excitatory neurotransmitters involved in pain signaling.[67] While effective for pain management, they do not specifically target oxidative stress mechanisms.[68]

*C. Opioids*: Although opioids are effective for various types of pain, their use in neuropathic pain is controversial due to the risk of addiction and tolerance.[69] Nevertheless, opioids like tramadol and oxycodone are sometimes prescribed, especially when other treatments fail.[69] Tramadol, in particular, also acts as a serotonin-norepinephrine reuptake inhibitor, providing additional pain relief by modulating descending inhibitory pathways.[69] Opioids primarily alter pain perception and do not address oxidative stress pathways.[70]

*D. Topical agents*: Topical treatments such as lidocaine

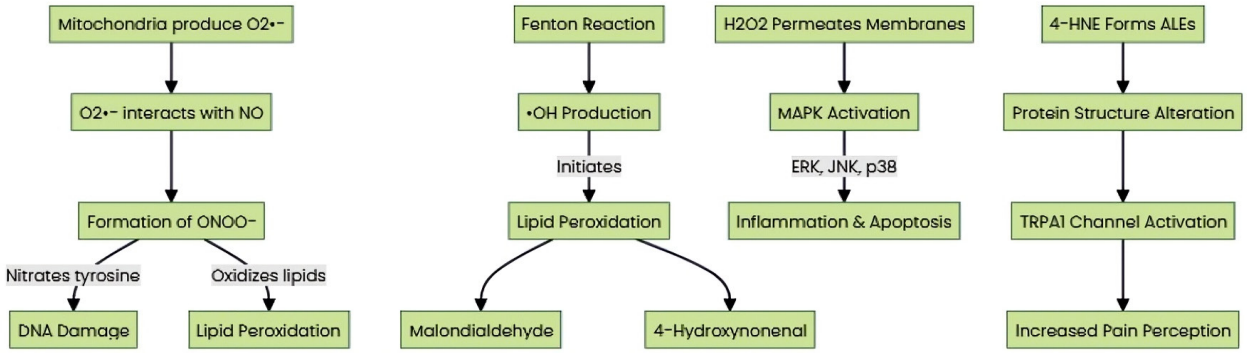


**Fig. 2.** Mechanisms of free radicals and oxidants in the development and progression of neuropathic pain. Key molecules involved in oxidative stress, including superoxide anion, hydroxyl radical, hydrogen peroxide, and 4-hydroxynonenal, contribute to neuropathic pain by disrupting cellular homeostasis and activating inflammatory and pain-signaling pathways.

patches and capsaicin cream provide localized pain relief with minimal systemic side effects.[71] Lidocaine acts as a sodium channel blocker, stabilizing neuronal membranes and inhibiting ectopic discharges.[71] Capsaicin, derived from chili peppers, depletes substance P from sensory nerve endings, gradually reducing pain transmission.[72] These agents act locally and are not directly involved in systemic oxidative stress.[72]

### *Non-pharmacological therapies*

*A. Physical Therapy*: Exercise and physical therapy can improve mobility, strength, and pain in individuals with neuropathic pain.[73] Techniques like transcutaneous electrical nerve stimulation (TENS) deliver electrical impulses through the skin, interfering with pain signaling pathways and providing temporary relief.[74] Physical activity has been shown to reduce oxidative stress levels, though this is not the primary mechanism of its analgesic effect.[74]

*B. Psychological Interventions*: Cognitive-behavioral therapy (CBT) is frequently employed to help patients manage chronic pain by altering pain perception and developing coping strategies.[75] Psychological support can reduce the emotional burden of chronic pain, thereby improving overall quality of life.[76] Stress reduction through psychological interventions may indirectly influence oxidative stress levels.[77]

*C. Interventional Procedures*: Invasive techniques such as nerve blocks, spinal cord stimulation (SCS), and intrathecal drug delivery systems are reserved for refractory cases of neuropathic pain.[78] SCS involves the implantation of a device that delivers electrical pulses to the spinal cord, modulating pain signals before they reach the brain.[79] Intrathecal pumps deliver medication directly to the spinal fluid, allowing for lower doses and fewer systemic side effects.[79] These interventions primarily focus on altering pain transmission pathways rather than addressing oxidative stress.[80]

*D. Acupuncture*: This traditional Chinese medicine technique involves inserting fine needles into specific points on the body to stimulate nerves, muscles, and connective tissue.[81] Acupuncture is believed to enhance the body's natural painkillers and increase blood flow, providing pain relief for some patients.[82] There is some evidence that acupuncture may reduce oxidative stress markers, though this is not its primary mechanism of action.[83,84]

## MSCs as a new therapeutic platform in neuropathic pain management

MSCs are multipotent stromal cells with the ability to differentiate into various cell types, including osteoblasts, chondrocytes, and adipocytes.[85] While commonly isolated from bone marrow, MSCs can also be sourced from adipose tissue, umbilical cord blood, placenta, and dental pulp.[85] These cells are characterized by their adherence to plastic in culture, expression of surface antigens such as CD73, CD90, and CD105, and the absence of hematopoietic markers like CD34, CD45, and CD14.[85] These features enable their broad application in regenerative medicine. MSCs exhibit a unique capacity to home to sites of injury or inflammation, interact with immune cells, and display potent immunomodulatory properties.[86] Additionally, MSCs secrete various bioactive molecules that promote tissue repair and regeneration, positioning them as promising candidates for conditions like neuropathic pain, where inflammation and tissue damage are central to the disease pathology.[87] In oxidative stress-mediated neuropathic pain, MSCs' antioxidative properties, including the secretion of antioxidant enzymes and molecules, further underscore their therapeutic potential.[87]

The source of MSCs in clinical studies is crucial, as each source presents unique advantages and challenges. Bone marrow-derived MSCs (BM-MSCs), harvested from the iliac crest, are extensively studied and have demonstrated efficacy in various therapeutic applications.[88] However, the invasive nature of their extraction is a limitation. BM-MSCs are known for their robust proliferative and differentiation capacities, making them the gold standard in MSC research.[89] In contrast, adipose-derived MSCs (AD-MSCs), which can be obtained through less invasive procedures such as liposuction, are abundant and share similar functional properties with BM-MSCs, with added advantages in accessibility and yield.[90] AD-MSCs exhibit significant anti-inflammatory and immunomodulatory effects, enhancing their potential in treating inflammatory and oxidative stress-related neuropathic pain.[90] Umbilical cord-derived MSCs (UC-MSCs), sourced from Wharton's jelly, offer another promising option due to their high proliferative capacity and low immunogenicity, making them ideal for allogeneic transplantation.[91] UC-MSCs, collected non-invasively, possess potent therapeutic properties, including reducing oxidative stress and promoting neuronal repair, making them particularly attractive for clinical applications.[92] Similarly, placenta-derived MSCs, also collected post-partum, exhibit strong regenerative potential and immunomodulatory effects.[93] These cells secrete a variety of cytokines and growth factors that mitigate oxidative damage and support tissue regeneration, further reinforcing their viability for neuropathic pain management.[94]

Pre-clinical studies in animal models have demonstrated the therapeutic potential of MSCs for alleviating neuropathic pain. MSCs possess potent anti-inflammatory properties critical for managing neuropathic pain.[95] Studies by Miyano et al and Chen et al demonstrated that AD-MSCs and UC-MSCs reduce inflammation by modulating cytokine levels and suppressing neuroinflammation, respectively.[95,96] Research by Evangelista et al), Yoo et al, and Siniscalco et al further supports MSCs' ability to mitigate neuropathic

pain by decreasing oxidative stress and inflammation in animal models.[97-99] The pain-relieving effects of MSCs are primarily mediated through the reduction of pro-inflammatory molecules and the inhibition of excessive glial cell activation, both pivotal processes in the pathophysiology of neuropathic pain.[99]

The reduction of oxidative stress is another critical mechanism by which MSCs exert their therapeutic effects. Elevated oxidative stress levels contribute significantly to neuronal damage, a key factor in the development of neuropathic pain.[100] Studies by Oliveira et al and Zhang et al demonstrated that MSCs can restore redox homeostasis and decrease oxidative stress markers.[101] MSCs achieve this by upregulating key antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), mitigating ROS production and enhancing neuronal health.[102] Further research, such as studies by Xu et al and Motegi et al, identified NADPH oxidase 2 (NOX2)-driven oxidative stress in dorsal root ganglion (DRG) neurons as a significant contributor to neuropathic pain.[103,104] These studies suggest that inhibiting NOX2 and reducing ROS production can attenuate neuronal hyperexcitability and mechanical allodynia, emphasizing oxidative stress management as a therapeutic target.[103,104]

MSCs also play a crucial role in neuroprotection and nerve regeneration, both essential for functional recovery in neuropathic pain.[105] Shiue et al demonstrated that MSC-derived extracellular vesicles (EVs) promote nerve regeneration by upregulating axon regeneration markers such as GAP-43.[106] Similarly, Miyano et al and Luo et al provided evidence that MSCs promote remyelination and offer neuronal protection against oxidative damage.[95,107] These findings underscore MSCs' potential to enhance neuroregenerative processes and preserve neuronal integrity, contributing to neuropathic pain relief.

Moreover, MSCs modulate pain signaling pathways, which play a pivotal role in neuropathic pain.[108] Studies by Yamazaki et al, Watanabe et al, and Lee et al demonstrated that MSCs influence critical pathways, including the MAPK pathways, involved in pain hypersensitivity.[109-111] Additional research by Waterman et al and Sacerdote et al reported that MSCs and adipose-derived stem cells (hASCs) reduce neuropathic pain and inflammation in animal models by secreting bioactive factors and modulating the local immune response.[112,113] This modulation results in a decrease in neuronal hyperexcitability and the preservation of pain suppression mechanisms, further supporting the use of MSCs in neuropathic pain management.[108-113]

## Functional mechanisms of MSCs in modulation and alleviation neuropathic pain

Neuropathic pain, often chronic and debilitating, arises from nerve damage and is typically accompanied by symptoms such as allodynia and hyperalgesia.[15] Oxidative stress, characterized by an imbalance between the production of ROS and the body's ability to neutralize these reactive intermediates, plays a pivotal role in the pathogenesis of neuropathic pain.[15] Recent advancements in regenerative medicine suggest that MSCs hold significant promise as a therapeutic option for addressing neuropathic pain, particularly through their antioxidative properties.[114]

MSCs target multiple pathophysiological mechanisms underlying neuropathic pain. A key therapeutic benefit of MSCs is their immunomodulatory effect, enabling them to suppress the inflammatory responses that exacerbate neuropathic pain.[115] MSCs accomplish this by secreting anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), which help mitigate the pro-inflammatory environment surrounding damaged nerves.[116] Furthermore, MSCs demonstrate strong antioxidant activity, acting as scavengers of ROS and enhancing the production of endogenous antioxidant enzymes, including SOD, catalase, and glutathione peroxidase.[117] This multifaceted antioxidant defense system effectively reduces oxidative stress at the site of nerve injury, thereby contributing to pain relief.[118]

In addition to their immunomodulatory and antioxidant properties, MSCs provide neuroprotective and neuroregenerative benefits. They secrete neurotrophic factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF), which are essential for nerve repair and regeneration.[119,120] By promoting neuroregeneration and reducing oxidative stress, MSCs enhance the recovery of damaged nerves and alleviate neuropathic pain.[117] Moreover, MSCs modulate the activity of glial cells, particularly microglia and astrocytes, which play critical roles in the maintenance of neuropathic pain.[121] Microglial activation, often driven by oxidative stress, contributes to inflammation and neuronal sensitization, thereby exacerbating pain.[122] MSCs attenuate neuropathic pain by regulating glial cell function and diminishing their pro-inflammatory and pain-promoting activities.[122]

Beyond their direct role in scavenging ROS, MSCs also modulate oxidative stress through indirect mechanisms.[123,124] They secrete antioxidants such as glutathione and thioredoxin, and their paracrine signaling enhances the antioxidant defenses of surrounding tissues, promoting resilience to oxidative stress and facilitating tissue repair.[125] This combination of direct ROS scavenging and the enhancement of endogenous antioxidant defenses underscores the therapeutic potential of MSCs in treating oxidative stress-mediated neuropathic pain.[125]

## The effective factors on MSCs' efficacy in therapeutic applications

### *Route and timing of administration*

The route and timing of MSC administration are pivotal

factors determining the efficacy of MSC-based therapies for neuropathic pain.[126] Intrathecal administration of MSCs has been shown to significantly attenuate neuropathic pain behaviors and oxidative stress, as demonstrated in studies by Zhang et al and Chen et al.[99,108] Additionally, the timing of MSC transplantation is critical; early post-injury intervention has been associated with enhanced therapeutic outcomes. Watanabe et al reported that early MSC transplantation post-injury not only improves motor function but also reduces pain hypersensitivity more effectively by promptly modulating inflammatory and oxidative stress pathways.[122] This underscores the importance of optimizing both the delivery route and the timing of MSC administration to maximize therapeutic benefits in neuropathic pain management.

### *MSC source and genetic engineering*

MSCs can be derived from various sources, including BM-MSCs, AD-MSCs, and UC-MSCs,[127] with the therapeutic efficacy of these populations exhibiting significant variability.[128] For instance, Yousefifard et al demonstrated that UC-MSCs show superior survival rates and more favorable electrophysiological outcomes compared to BM-MSCs,[129] suggesting that UC-MSCs may be more advantageous for specific therapeutic applications.

In addition to source-dependent variations, genetic engineering of MSCs has emerged as a potent strategy to enhance their therapeutic potential.[130] Yu et al showed that genetic modifications can optimize MSC efficacy by increasing the secretion of therapeutic peptides, such as glial cell line-derived neurotrophic factor (GDNF).[131] These advancements in genetic engineering hold promise for developing more effective MSC-based therapies for combating oxidative stress-mediated neuropathic pain.[130]

## New MSC-based therapeutic approaches for neuropathic pain

### *Combination therapies*

Combining MSC therapy with conventional pharmacological treatments offers a promising avenue for augmenting therapeutic efficacy in neuropathic pain.[24] This approach leverages the unique properties of MSCs, including their ability to dampen inflammation, promote tissue repair, and modulate oxidative stress, while potentially synergizing with the established mechanisms of existing medications.[132]

A compelling example of this synergy is the study by Yousof et al, which demonstrated that co-administration of AD-MSCs with pregabalin resulted in a more pronounced reduction in inflammation and enhanced nerve function compared to monotherapy with either treatment alone.[133] This finding suggests that MSCs may amplify the analgesic and anti-inflammatory properties of pregabalin, leading to a more robust therapeutic effect.

Beyond pregabalin, the exploration of combination therapies with other drug classes is ongoing.[134] Studies suggest that co-administration of MSCs with antioxidant therapies may offer a particularly potent approach.[129] Ma et al reported that combining BM-MSCs with N-acetylcysteine (NAC), an antioxidant, resulted in superior pain relief and improved functional recovery in a chronic sciatic nerve injury model compared to either treatment alone.[135] This synergistic effect likely stems from the combined action of MSCs in reducing inflammation and promoting tissue repair, alongside NAC's direct ROS scavenging activity.[135]

Another promising avenue is the combination of MSC therapy with gene therapy vectors that deliver neurotrophic factors or anti-inflammatory molecules. Nolta demonstrated that BM-MSCs genetically modified to express BDNF exhibited enhanced efficacy in alleviating neuropathic pain and promoting nerve regeneration in a diabetic neuropathy model.[136] This approach leverages the inherent therapeutic properties of MSCs while offering targeted delivery of additional beneficial factors.

### *Extracellular vesicles: A cell-free frontier*

MSC-derived EVs represent a burgeoning therapeutic frontier with immense potential for managing oxidative stress-mediated neuropathic pain.[137] Unlike cell-based therapies using MSCs directly, EVs offer a cell-free alternative that overcomes several limitations associated with live cell administration, including challenges in cell expansion, potential tumorigenicity, and the logistical complexities of cell delivery.[138]

Studies by Luo et al and Shiue et al highlight the therapeutic promise of MSC-EVs.[118,119] Their findings demonstrate that MSC-EVs possess potent antioxidant and neuroprotective properties.[118,119] This therapeutic potential is largely attributed to their rich cargo of bioactive molecules, including microRNAs (miRNAs) and proteins, which modulate cellular pathways involved in oxidative stress and promote neuronal repair.[118,119]

## Conclusion and Future Directions

The burgeoning body of research underscores the multifaceted therapeutic potential of MSCs in addressing neuropathic pain precipitated by oxidative stress. MSCs exhibit a complex interplay of mechanisms, encompassing the attenuation of inflammation, mitigation of oxidative damage, and neuronal protection. To harness their full therapeutic potential, future research must focus on optimizing delivery methods, determining precise dosages, and identifying the most efficacious sources of MSCs. Additionally, the exploration of MSC-derived EVs presents a promising avenue, potentially enhancing therapeutic efficacy. Investigating synergistic effects through combination therapies with existing pain medications could further refine treatment protocols. To translate these promising preclinical findings into viable

## Review Highlights

**What is the current knowledge?**

- Neuropathic pain arises from damage to the somatosensory system, leading to chronic discomfort.
- Oxidative stress is a critical factor in neuropathic pain, damaging neurons and amplifying pain signals.
- Traditional therapies for neuropathic pain are often inadequate and focus on symptom relief rather than the underlying causes.

**What is new here?**

- Mesenchymal stem cells (MSCs) offer a novel therapeutic approach, targeting oxidative stress in neuropathic pain.
- MSCs have shown potential in reducing oxidative damage, promoting neuroregeneration, and modulating immune responses.
- This study emphasizes the multifaceted role of MSCs, particularly their antioxidative properties, in alleviating neuropathic pain.

clinical applications, rigorous and well-designed clinical trials are imperative, aiming to establish MSC-based therapies as a cornerstone in the management of chronic neuropathic pain.

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### Authors' Contribution

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**Investigation:** Aidin Shahrezaei.
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### Competing Interests

The authors declare that they have no competing interests.

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Data are available from Aidin Shahrezaei upon reasonable request.

### Ethical Approval

Not applicable.

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