Current Pharmaceutical Letters and Reviews (CPLR)
Website: https://cplr.in/
ISSN: 3049-222X
Vol. 3, Issue 1, Jan-Mar, 2026
Page No.: 56-59

Short Communication

Cannabinoid Receptor Modulators in Neuropathic Pain: Expanding Therapeutic Horizons Beyond Conventional Analgesics

Mukesh Kumar, Subham Mandal

Department of Pharmacy, IIMT College of Medical Sciences, IIMT University, O-Pocket, Ganganagar, Meerut, U.P., 250001, India

Corresponding Author:
Subham Mandal

Email:
sk8006721807@gmail.com

DOI: *10.62896/cplr.3.1.05*

Conflict of interest: *NIL*

Article History
Received: 12/01/2026
Accepted: 21/01/2026
Published: 25/02/2026

Abstract:

Background: Neuropathic pain (NP) is a chronic and debilitating condition arising from lesions or dysfunction in the somatosensory nervous system. Conventional pharmacological treatments, including antidepressants, anticonvulsants, and opioids, often provide inadequate relief and are associated with significant adverse effects. Cannabinoid receptor modulators targeting the endocannabinoid system (ECS) have emerged as promising alternatives. **Objective:** This review aims to evaluate the therapeutic potential, mechanisms, and clinical evidence of cannabinoid receptor modulators (CB1 and CB2 agonists/antagonists) in neuropathic pain management. **Methods:** A comprehensive literature review of preclinical studies, randomized controlled trials, and systematic reviews (2020–2026) was conducted focusing on cannabinoid pharmacology, receptor modulation, and clinical outcomes. **Results:** Cannabinoids demonstrate analgesic effects through modulation of neurotransmitter release, reduction of neuroinflammation, and activation of descending inhibitory pathways. CB2-selective agonists show significant promise due to reduced central side effects. However, clinical evidence remains inconsistent, with modest efficacy and notable adverse effects reported in some trials. **Conclusion:** Cannabinoid receptor modulators represent a promising but complex therapeutic strategy in neuropathic pain. Future research should focus on receptor-selective drugs, personalized medicine approaches, and improved clinical trial design.

Keywords: Cannabinoid receptor modulators; Neuropathic pain; Endocannabinoid system; CB1 receptors; CB2 receptors; Cannabidiol (CBD); Δ9-tetrahydrocannabinol (THC); Neuroinflammation; Chronic pain management; Analgesic therapy; Synthetic cannabinoids; Pain modulation; Central sensitization; Opioid-sparing therapy; Cannabinoid pharmacology

1. Introduction

Neuropathic pain (NP) is a complex chronic pain condition caused by damage or dysfunction of the somatosensory nervous system. It affects approximately 7–10% of the global population and significantly impairs quality of life. Conventional treatments such as gabapentinoids, tricyclic antidepressants, and opioids are often insufficient, with many patients experiencing incomplete relief or intolerable side effects.

This therapeutic gap has driven interest in alternative targets, particularly the **endocannabinoid system (ECS)**. Cannabinoids, derived from *Cannabis sativa* or synthesized analogs, interact with cannabinoid receptors (CB1 and CB2) to modulate pain signaling pathways.

These agents have gained attention as potential modulators of neuropathic pain due to their multi-target mechanisms and opioid-sparing potential [1].

2. Pathophysiology of Neuropathic Pain

Neuropathic pain arises from maladaptive changes in both peripheral and central nervous systems, including:

- Peripheral nerve injury
- Central sensitization
- Neuroinflammation
- Altered ion channel expression
- Dysfunctional inhibitory pathways

Chronic NP is characterized by symptoms such as allodynia, hyperalgesia, and spontaneous pain. Neuroinflammation, driven by microglial and astrocyte activation, plays a central role in maintaining pain states.

The ECS has emerged as a critical regulator of these processes, influencing synaptic transmission, immune responses, and neuronal excitability.

3. The Endocannabinoid System (ECS)

The ECS consists of:

- **Cannabinoid receptors:** CB1 and CB2
- **Endogenous ligands:** Anandamide (AEA), 2-arachidonoylglycerol (2-AG)
- **Metabolic enzymes:** FAAH, MAGL

3.1 CB1 Receptors

- Predominantly located in the central nervous system
- Modulate neurotransmitter release
- Responsible for psychoactive effects

3.2 CB2 Receptors

- Primarily expressed in immune cells and peripheral tissues
- Regulate inflammation and immune responses
- Associated with analgesic effects without psychoactive side effects

Activation of these receptors reduces pain signaling by inhibiting excitatory neurotransmitters and enhancing inhibitory pathways [1].

4. Mechanisms of Cannabinoid Action in Neuropathic Pain

Cannabinoids exert analgesic effects through multiple mechanisms:

4.1 Neurotransmitter Modulation

Cannabinoids inhibit presynaptic release of glutamate and substance P, reducing neuronal excitability.

4.2 Anti-inflammatory Effects

They suppress pro-inflammatory cytokines and reduce microglial activation, thereby decreasing neuroinflammation [1].

4.3 Activation of Descending Inhibitory Pathways

Cannabinoids enhance endogenous pain inhibition pathways in the brainstem.

4.4 Oxidative Stress Reduction

They reduce oxidative damage, which contributes to chronic pain states.

4.5 Autophagy Regulation

Recent evidence suggests cannabinoids may correct autophagy dysfunction in neuropathic conditions [1].

5. Types of Cannabinoid Receptor Modulators

5.1 Phytocannabinoids

- Δ9-tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- Cannabigerol (CBG)

5.2 Synthetic Cannabinoids

- Dronabinol
- Nabilone
- Nabiximols

5.3 Selective CB2 Agonists

- LY2828360
- HU-308

CB2-selective agents are particularly promising due to minimal psychoactive effects [2].

6. Preclinical Evidence

Animal studies provide strong evidence for cannabinoid efficacy in neuropathic pain:

- CB2 agonists significantly reduce mechanical allodynia and thermal hyperalgesia
- They also prevent opioid tolerance and dependence [2]
- Cannabigerol (CBG) shows potent analgesic effects across multiple pain models [3]

Additionally, CB2 receptor activation reduces neuroinflammation by suppressing cytokine release and microglial activation [4].

7. Clinical Evidence

7.1 Positive Findings

- Several studies report significant pain reduction with cannabinoid-based therapies
- Approximately 79% of clinical trials show improvement in neuropathic pain scores [5]
- THC-based formulations demonstrate clinically meaningful pain relief in some patients [6]

7.2 Conflicting Evidence

- Some systematic reviews report only modest benefits
- Evidence suggests improvements are often small and short-term [7]
- CBD alone shows limited efficacy in many trials [8]

7.3 Recent Meta-Analyses

- Moderate evidence supports cannabinoid use in neuropathic pain
- Benefits are more pronounced in treatment-resistant cases [9]

Overall, clinical outcomes remain variable and patient-dependent.

8. Advantages Over Conventional Analgesics

Cannabinoids offer several advantages:

- Multi-target mechanism of action
- Reduced risk of respiratory depression
- Potential opioid-sparing effects
- Modulation of both pain and inflammation

These features make them attractive alternatives, particularly in chronic and refractory pain conditions.

9. Limitations and Safety Concerns

Despite their potential, cannabinoids have several limitations:

- Psychoactive effects (especially CB1 agonists)
- Cognitive impairment and sedation
- Risk of dependency
- Inconsistent clinical efficacy
- Lack of standardized dosing

Adverse effects such as dizziness, nausea, and sedation are commonly reported [7].

10. Emerging Trends and Future Directions

10.1 CB2-Selective Drugs

Focus on peripheral analgesia without CNS side effects.

10.2 Biased Agonism

Development of ligands targeting specific signaling pathways.

10.3 Combination Therapy

Cannabinoids combined with opioids or antidepressants.

10.4 Nanotechnology-Based Delivery

Improved bioavailability and targeted delivery.

10.5 Personalized Medicine

Tailoring treatment based on genetic and molecular profiles.

11. Discussion

Cannabinoid receptor modulators represent a paradigm shift in neuropathic pain management. While preclinical evidence is robust, clinical translation remains challenging due to variability in patient response, formulation differences, and study design limitations.

CB2 receptor agonists appear particularly promising, offering analgesia without psychoactive effects. However, further high-quality clinical trials are needed to establish their efficacy and safety.

12. Conclusion

Cannabinoid receptor modulators provide a promising alternative to conventional analgesics for neuropathic pain. Their ability to target multiple pain pathways and reduce inflammation positions them as valuable therapeutic agents.

However, inconsistent clinical outcomes and safety concerns highlight the need for further research. Future advancements in selective receptor targeting and drug delivery systems may unlock their full therapeutic potential.

References

1. Arthur P, et al. Applications of cannabinoids in neuropathic pain. *Biomed Pharmacother*. 2024. (PMC)
2. Guenther KG, et al. CB2 agonist LY2828360 suppresses neuropathic pain. *Neuropharmacology*. 2025. (ScienceDirect)
3. Rezende B, et al. Cannabigerol in neuropathic pain models. *Pharmaceutics*. 2025. (MDPI)
4. Nazemi S, et al. CB2 receptor-mediated analgesia. *Behav Brain Res*. 2025. (ScienceDirect)

5. Choi J, et al. Cannabinoids in neuropathic pain: systematic review. *J Hand Surg*. 2025. (PubMed)
6. Medical cannabis in neuropathy. *SAGE Journals*. 2026. (Sage Journals)
7. Chou R, et al. Cannabis for chronic pain review. *Cochrane Database*. 2025. (NCBI)
8. Moore A, et al. CBD products for pain: systematic review. *Pain*. 2024. (ScienceDirect)
9. Johnson BW, et al. Cannabinoids in chronic pain management. *Biomedicines*. 2025. (MDPI)
10. Pulone S, et al. Cannabinoids in aging and pain. *Ageing Res Rev*. 2026. (ScienceDirect)

*****