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# Chemotherapeutic induced neuropathic pain: A review from the literature focusing on its treatments

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## Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating adverse effect of many anticancer agents, presenting with sensory symptoms such as spontaneous pain and mechanical or cold allodynia in a characteristic "stocking and glove" distribution. This neuropathic pain can severely limit the dosage and duration of life-saving chemotherapy, often necessitating treatment modification or cessation, and may persist long after therapy, impairing survivors' quality of life. Standard pharmacological treatments offer limited efficacy, highlighting the need for alternative therapies. This review summarizes current literature on emerging treatments for CIPN, with a focus on three agents: nabiximols, gabapentin, and phenyl N-tert-butylnitrone (PBN). Nabiximols, a cannabinoid-based oral spray, demonstrated modest efficacy and a favorable safety profile in a small pilot study, suggesting the need for larger clinical trials. Gabapentin, an anticonvulsant, showed potential as an early intervention in patients with mild symptoms, with good tolerability and safety. PBN, a potent free radical scavenger, prevented the development of neuropathic pain in preclinical models of paclitaxel-induced neuropathy, offering promising neuroprotective effects. Collectively, these findings underscore the importance of further clinical and translational research to identify and validate effective therapies for managing CIPN.

**Keywords:** CIPN, Gabapentin, Neuropathic, Anticonvulsant.

## 1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent and debilitating adverse effect associated with numerous anticancer agents. Characterized by sensory disturbances such as spontaneous pain, mechanical and cold allodynia, CIPN typically presents in a "stocking and glove" distribution, affecting both hands and feet. This condition significantly impairs patients' functional capacity and quality of life, thereby posing substantial challenges to the delivery of optimal cancer care.[1]

The development of CIPN often necessitates modification of chemotherapy regimens, including dose reductions, treatment delays, or the substitution of less effective therapeutic agents. In severe cases, it may lead to premature discontinuation of potentially curative treatments. The persistence of neuropathic symptoms long after the cessation of chemotherapy further exacerbates the burden on cancer survivors, contributing to long-term morbidity and diminished quality of life.[2]

CIPN is most frequently associated with chemotherapeutic agents such as paclitaxel, vincristine, and cisplatin. These drugs induce alterations in peripheral and central nervous system function, leading to heightened nociceptive sensitivity and pain transmission. Specifically, they sensitize spinal cord neurons involved in the processing of pain, thereby amplifying nociceptive signaling. Despite its high prevalence and significant clinical impact, CIPN remains poorly responsive to standard pharmacological treatments, including opioids,

antidepressants, and anticonvulsants. This underscores a critical unmet need for effective and well-tolerated therapeutic strategies.[3,4]

Currently, no pharmacologic agents have received widespread clinical endorsement for the prevention or treatment of CIPN. Although several compounds—such as nerve growth factor, insulin-like growth factor I, and amifostine—have demonstrated neuroprotective properties in preclinical or early clinical studies, none have shown sufficient efficacy or safety in large-scale trials to warrant routine clinical use.[5–7]

In recent years, preclinical research has highlighted the potential of cannabinoid receptor agonists in alleviating neuropathic pain associated with chemotherapy. These agents have shown efficacy in attenuating established pain behaviours in animal models of CIPN. The cannabinoid system, through modulation of nociceptive signalling at both peripheral and central levels, offers a promising therapeutic target. Given the limitations of existing treatments and the increasing population of cancer survivors, further investigation into cannabinoid-based interventions for CIPN is warranted.[8,9]

## 2. Drug used for the treatment of CNIP

### 2.1. Nabiximols

Examine the action of a currently available cannabinoid in the treatment of chemotherapy-induced neuropathic pain.

#### 2.1.1 Study design:

A randomized, placebo-controlled, crossover pilot study examining an oral mucosal spray containing cannabinoids (nabiximols [Sativex, GW Pharmaceuticals, U.K.) in 18 patients with established chemotherapy induced neuropathic pain was performed.

#### 2.1.2 Outcome:

When examining the whole group, there was no statistically significant difference between the treatment and the placebo groups. Responder analysis nonetheless demonstrated that five participants reported a two-point or greater reduction in their pain according to NRS-PI, which trended toward statistical significance. NNT was five. The fact that in this statistically underpowered small pilot trial there were five participants who experienced a clinically significant (two-point or greater) reduction in their pain makes it worthwhile to carry out a larger randomized controlled trial examining nabiximols in this population.

Ten participants who chose to continue into the extension phase all noted modest improvements, with several noting further improvement beyond the initial pain reduction. This trial also demonstrated that nabiximols is a safe medication. There were no serious adverse events and the adverse events experienced were mild and transient and did not lead to withdrawal from the study or discontinuation of the medication.

### 2.2 Gabapentin

Gabapentin is an anticonvulsant, structurally related to gamma-aminobutyric acid (GABA) used in the ailments of various diseases, little is known about its use as a monotherapy in the setting of CIPN**.**

#### 2.2.1 Study design:

After enrolment in the study, patients underwent a complete physical examination (including a thorough neurologic evaluation), and a basic labora-tory work-up, including a complete blood count and a comprehensive metabolic panel. Side effects were monitored and laboratory work-up was repeated before the administration of each cycle. All patients were followed closely for the development of neuropathic pain. When neuropathic symptoms developed during the study period, the dosage of the administered cytostatic drugs was kept constant and gabapentin therapy was initiated; if these symptoms worsened during subsequent cycles, neurotoxic chemotherapy was administered at lower doses or discontinued. The study protocol was reviewed and approved by the ethics committees of the participating hospitals. All patients gave written informed consent.[10,11]

#### 2.2.2 Results:

Our results show that a fixed low-dose of gabapentin can be of value in the management of chemotherapy-induced neuropathic pain. An important finding is that its effectiveness is maximized when it is used in patients without severe baseline neuropathic pain, implying that it should be considered early, rather than late, in the therapeutic algorithms. We also confirm that gabapentin is an extremely safe and well-tolerated medication as no patient discontinued it because of side effects.

### 2.3. Phenyl N-tert-butylnitrone

Phenyl N-tert-butylnitrone (PBN) is a spin-trap reagent and a potent free radical scavenger. However, the effect of PBN on chemotherapy-induced neuropathic pain has not been reported.

**2.3.1 Study design:**

The research examines a paclitaxel-induced neuropathic pain model in rats, emphasizing the application of PBN (Phenyl N-tert-butylnitrone) as a prospective preventative intervention. Various methodologies were investigated, encompassing multiple PBN injections in healthy rats, alongside both single and multiple PBN injections intended to avert paclitaxel-induced neuropathic discomfort. Behavioural tests were performed to evaluate mechanical allodynia, a critical measure of neuropathic pain, in order to determine the efficacy of these therapies.

**2.3.2 Outcomes:**

After intraperitoneal injection of PBN in rats, it swiftly propagates to all organs, including the brain, spinal cord, and liver, within 20 minutes, and is subsequently eliminated in urine, exhibiting a half-life of roughly 134 minutes. Consequently, the sites of action of PBN include organs inside both the central nervous system (brain and spinal cord) and the peripheral nervous system (sensory nerves, dorsal root ganglia, and nerve terminals). Repeated injections of PBN from days 7 to 15 entirely inhibited the onset of paclitaxel-induced neuropathic pain in rats.

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