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Topical medicines in chemotherapy-induced peripheral neuropathy

Karolina Pawelec[1*], Sabina Jóźwiak[1], Karolina Iwanicka[1], Ewelina Wesołek-Bielaska[2], Katarzyna Szklener[2], Sławomir Mandziuk[2*]

[1] Student Academic Group, Department of Clinical Oncology and Chemotherapy, Medical University of Lublin, Poland
[2] Department of Clinical Oncology and Chemotherapy, Medical University of Lublin, Poland

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ABSTRACT

Oncology patients face numerous challenges resulting both from their underlying disease and from the adverse effects of anticancer treatment. Chemotherapy-induced peripheral neuropathy (CIPN) is among the most serious complications associated with chemotherapy. The sensory and motor disturbances observed in the course of CIPN are often progressive and may be irreversible, while severe and chronic pain leads to a substantial reduction in patients' quality of life (QoL).

This narrative review summarizes currently available topical treatment options for CIPN, focusing on substances that have shown potential clinical benefit. The pathogenesis of CIPN remains incompletely understood, and existing treatment strategies are frequently insufficient or associated with significant adverse effects. Consequently, both the prevention and management of CIPN remain important challenges in contemporary medicine.

Recently, increasing attention has been directed toward topically administered agents, including formulations based on phenytoin, lidocaine, amitriptyline, capsaicin, cannabinoids, duloxetine, ketamine, and baclofen. These therapies may alleviate neuropathic symptoms and improve QoL without the systemic complications commonly associated with oral or intravenous pharmacotherapy. The use of topical medications may also allow for a reduction in systemic analgesic doses and is often favored due to their more favorable safety profile. Therefore, topical agents should be considered promising therapeutic options aimed at minimizing systemic side effects and optimizing the current pharmacological management of patients with CIPN.

INTRODUCTION

The International Association for the Study of Pain defines neuropathic pain as pain caused by a lesion or disease of the somatosensory nervous system, affecting either the peripheral and/or central components. This condition may manifest as loss of sensory function or altered sensation, as well as increased sensitivity to pain or spontaneous pain [1]. Oncological conditions represent a significant cause of neuropathic pain. These include tumors that directly damage the nervous system due to primary tumor growth or metastatic spread, as well as neuropathies resulting from cancer treatment modalities such as surgery, chemotherapy, and radiotherapy [2].

* **Corresponding author**
e-mail: katarzyna.szklener@umlub.edu.pl

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most serious complications associated with treatment using neurotoxic anticancer agents [3]. It is estimated to affect approximately 30-60% of patients undergoing cancer therapy [4]. CIPN leads to dysfunction of the sensory, motor, and autonomic nervous systems. A characteristic clinical feature is the typical distribution of sensory symptoms in a "stocking-and-glove" pattern. Symptoms usually begin in the fingers and toes and subsequently progress proximally to involve the limbs [3,5].

The predominant clinical manifestations include tingling, numbness, paresthesia, impaired vibration sense, and altered sensitivity to touch as well as to high or low temperatures. Motor symptoms occur less frequently and often present as muscle weakness, which may result in gait disturbances and impaired balance [6]. Among chemotherapeutic agents,

certain drug classes are particularly associated with the development of CIPN, including platinum-based compounds, taxanes, vinca alkaloids, eribulin, bortezomib, and thalidomide [7].

The risk of developing CIPN increases with higher cumulative doses, prolonged exposure, or combination chemotherapy regimens. Individual risk factors include advanced age, diabetes mellitus, hypothyroidism, vitamin deficiencies, smoking history, alcohol abuse, pre-existing peripheral neuropathy, renal dysfunction, infections, autoimmune rheumatic diseases, and genetic susceptibility, including single nucleotide polymorphisms [4,6,8,9].

The pathogenesis of CIPN is multifactorial and remains incompletely understood. Neurotoxic chemotherapeutic agents exert their effects on multiple structures, including the dorsal root ganglia, intraepidermal nerve fibers, axons, and cell bodies of sensory neurons of C fibers, wide dynamic range neurons (WDRNs) in the spinal cord, as well as central structures such as the thalamus and hypothalamus [10]. Axonal degeneration is a key pathological feature of CIPN [11].

Additional mechanisms involved in CIPN include disturbances in neuronal metabolism, particularly mitochondrial damage leading to oxidative stress, disruption of microtubules affecting axonal transport [12], dysfunction of ion channels (sodium, calcium, and potassium channels), increased expression of transient receptor potential vanilloid (TRPV), transient receptor potential ankyrin 1 (TRPA1), and N-methyl-D-aspartate receptors (NMDARs), abnormal discharges of nociceptive Aδ and C fibers, damage to the myelin sheath, and deoxyribonucleic acid (DNA) damage [10,13].

Neuroinflammation also plays a significant role in the development of CIPN and involves cytokine release, macrophage infiltration, and upregulation of pro-inflammatory mediators. Elevated levels of neurotransmitters such as serotonin and glutamate may further contribute to the development and persistence of painful CIPN [3,10,14,15]. Localized neuropathic pain has a substantial negative impact on patients' quality of life (QoL) [16].

Current pharmacological and non-pharmacological treatment strategies for CIPN often demonstrate limited efficacy or are associated with significant adverse effects. Consequently, local routes of drug administration are gaining increasing interest in pain management. Topical therapies are characterized by a favorable safety profile and a lower incidence of systemic side effects, including a reduced risk of drug-drug interactions and overdose. Topically applied medications exert their effects locally by targeting peripheral mechanisms involved in the pathogenesis of neuropathy [17]. Elderly patients, who frequently present with comorbidities and age-related alterations in drug metabolism, may particularly benefit from local pharmacotherapy [18]. In this review, we discuss topical agents with potential applicability in the treatment of CIPN.

TOPICAL MEDICINES IN PAIN TREATMENT

1. Phenytoin

Phenytoin, a hydantoin derivative, belongs to the class of anticonvulsant drugs and has been widely used in clinical practice for many years [19]. One of the novel therapeutic indications for phenytoin is the management of neuropathic pain [20]. It is a lipophilic compound with a molecular weight below 500 Daltons, which enables effective penetration through the stratum corneum of the epidermis [21].

When applied topically, phenytoin exerts several mechanisms of action. In addition to blocking voltage-gated sodium channels, it demonstrates immunomodulatory properties that may regulate peripheral inflammatory processes in small epidermal nerve fibers, thereby inhibiting hyperactivity of peripheral nerve endings [22].

In a cohort study, David J. Kopsky and Jan M. Keppel Hesselink described a group of 70 patients suffering from neuropathic pain of various etiologies, including individuals with CIPN, who were treated with 5% or 10% phenytoin cream. In this population, the mean onset time of analgesia was 16.3 minutes (standard deviation [SD]: 14.8), the mean duration of pain relief was 8.1 hours (SD: 9.1), and the mean reduction in pain intensity on the Numerical Rating Scale (NRS) was 61.2% (SD: 25.0). The average reduction in NRS score during treatment with phenytoin cream was statistically significant compared with baseline values and amounted to 4.5 points (95% confidence interval [CI]: 4.0-5.0; $p < 0.01$). In patients in whom plasma phenytoin concentrations were measured, levels remained below the detectable limit. Only two participants reported local adverse effects, consisting of transient burning sensation and mild skin rash. Additionally, a single-blind response test using 10% phenytoin cream versus placebo was conducted to identify responders to treatment. A statistically significant reduction in pain at the phenytoin-treated site compared with the placebo-treated site was observed [23].

These findings were further supported by subsequent studies conducted by Kopsky *et al*., in which a double-blind, placebo-controlled response test confirmed the rapid onset of analgesia following the application of 10% phenytoin cream in patients with polyneuropathy [21]. The same research group also reported two cases of patients with severe, difficult-to-treat CIPN. In one patient, the application of 5% phenytoin cream resulted in a noticeable reduction in tingling, burning pain, and a cooling sensation within 20 minutes, with pain intensity decreasing from 8 to 3 on the NRS. In the second case, a patient who developed persistent neuropathic pain in both hands and subsequently in the feet following bortezomib chemotherapy – accompanied by hypoesthesia and allodynia, leading to treatment discontinuation – experienced pain relief within 10-15 minutes after application of 10% phenytoin cream, with NRS scores decreasing from 7 to 0. The analgesic effect lasted up to 6 hours when the cream was applied twice daily. None of the patients reported local or systemic adverse effects. Moreover, the use of topical phenytoin allowed for a reduction in the doses of concomitant oral analgesics [20].

In another study, Jan M. Keppel Hesselink *et al*. described a patient with treatment-resistant CIPN in whom the application of 10% phenytoin cream resulted in complete pain relief within minutes, with the analgesic effect lasting up to 12 hours. Among six closely monitored patients using 10% phenytoin cream three times daily, four experienced a pain reduction exceeding 50%, while the remaining two

reported approximately 30% pain relief. The onset of analgesia ranged from 2 to 30 minutes, and the duration of pain relief varied between 2.5 and 70 hours. No adverse effects were reported, and plasma phenytoin levels measured several hours after application remained below the detection threshold. These findings suggest that topical phenytoin may represent a promising therapeutic option for the management of CIPN, particularly due to its rapid onset of analgesic action and favorable safety profile [22].

2. Lidocaine

Lidocaine is an amide-type local anesthetic and an antiarrhythmic agent classified as class Ib according to the Vaughan-Williams classification. Although it is commonly used in conduction anesthesia, lidocaine has also found application in the topical treatment of neuropathic pain [17].

Voltage-gated sodium channels (VGSCs) are expressed in many excitable cells, including peripheral and central neurons, as well as cardiac and skeletal muscle cells, where they play a crucial role in the initiation and propagation of action potentials. In sensory neurons, VGSCs determine electrical excitability and play a key role in pain perception by regulating the discharge of incoming nociceptive impulses. The VGSC family consists of nine isoforms (Nav1.1-Nav1.9), which differ in their physiological properties and expression patterns within the peripheral and central nervous systems [24].

Preclinical studies have demonstrated that chemotherapy-induced neuropathic pain is associated with dysfunction of specific VGSC subtypes. Nav1.7, Nav1.8, and Nav1.9 are highly expressed in nociceptors and therefore represent promising targets for local analgesic therapies. In models of neuronal injury, accumulation of Nav1.7 and Nav1.8 channels has been observed at sites of nerve damage. Consequently, increased VGSC expression has also been reported in patients with neuropathic pain. For this reason, lidocaine – a well-established local analgesic – has been widely used in the management of this type of pain [17,24].

The primary mechanism of action of lidocaine involves blockade of pathological sodium channels. These channels accumulate at sites of nerve injury and generate repetitive ectopic discharges, which exhibit a high affinity for lidocaine binding, resulting in inhibition of abnormal electrical activity. Notably, Nav1.8 is approximately five times more sensitive to lidocaine than Nav1.7 or other Nav subtypes [17].

Several topical lidocaine formulations have been developed; however, 5% lidocaine patches are the most widely registered and recommended [25]. Each 5% lidocaine patch contains 700 mg of lidocaine and allows for the simultaneous application of up to three patches for a maximum duration of 12 hours. Systemic absorption accounts for only 3% ± 2% of the maximum recommended dose, while more than 95% (approximately 665 mg) of lidocaine remains within the applied patch. After absorption, lidocaine binds primarily to alpha-1-acid glycoprotein and may cross the placental and blood-brain barriers by passive diffusion. The drug is metabolized in the liver to inactive metabolites, which are excreted by the kidneys. The elimination half-life is approximately 7.6 hours; however, dose adjustment is generally not required [26].

In addition to sodium channel blockade, topically applied lidocaine inhibits the release of pronociceptive mediators from keratinocytes, which constitute approximately 95% of epidermal cells. When administered in patch form, lidocaine also provides a cooling effect and mechanical protection of the affected skin areas [26,27]. The number needed to harm (NNH) for lidocaine patches is high (approximately 28), indicating a favorable safety profile. Consequently, topical lidocaine is recommended for the treatment of localized peripheral neuropathic pain [27].

Some clinical guidelines consider 5% lidocaine patches as a first-line treatment, particularly in elderly patients and those with frailty syndrome [28]. Due to their favorable safety profile, topical agents such as lidocaine patches may be preferred over systemic medications [27,29]. Although systemic absorption of topical lidocaine is minimal, its use is contraindicated in patients receiving class I antiarrhythmic drugs [30]. Clinical studies in patients with neuropathic pain have demonstrated that locally applied 5% lidocaine patches reduce all dimensions of neuropathic pain, as assessed by the Neuropathic Pain Scale, as well as allodynia. Overall, both preclinical and clinical evidence confirms the efficacy of topical lidocaine in painful neuropathic conditions [17]. Compared with placebo, lidocaine patches significantly reduce neuropathic symptoms and allodynia in patients with painful peripheral neuropathy [26].

3. Amitriptyline

Tricyclic antidepressants (including amitriptyline), serotonin-noradrenaline reuptake inhibitors (SNRIs) such as duloxetine, and anticonvulsants are among the most extensively studied drug classes in the treatment of neuropathic pain. Their effectiveness has been confirmed in numerous studies, with analgesic effects largely attributed to modulation of descending inhibitory pain pathways [31].

Amitriptyline hydrochloride is considered a first-line agent for the treatment of neuropathic pain. Its mechanisms of action include inhibition of serotonin and noradrenaline reuptake, blockade of voltage-gated sodium channels, and antagonism of muscarinic and histamine receptors. Despite extensive clinical use, the precise mechanism underlying its analgesic effects remains incompletely understood [31,32]. One proposed explanation involves increased concentrations of noradrenaline and serotonin in central synapses, which enhance descending inhibitory pain pathways and suppress ascending nociceptive transmission within the spinal cord [33].

Contraindications or conditions requiring particular caution with amitriptyline use include cardiovascular disease, glaucoma, benign prostatic hyperplasia, and seizure disorders. High doses should be avoided in individuals over 65 years of age and in patients with amyloidosis [31]. In addition to its therapeutic effects, oral amitriptyline is associated with systemic adverse effects such as sedation, cardiotoxicity, weight gain, and anticholinergic symptoms [31,32]. These adverse effects and related contraindications often limit dose escalation and prevent some patients from achieving optimal analgesia.

A potential strategy to minimize systemic adverse effects while maintaining therapeutic efficacy is the topical application of amitriptyline in cream form, typically at a concentration of 10% [32]. In a study conducted by Genevois *et al*., 25 patients with CIPN affecting the hands, feet, or both were treated with 10% topical amitriptyline for one month. In seven patients, CIPN developed during an effective anticancer treatment, while in the remaining patients neuropathy persisted long after chemotherapy completion. At baseline, all patients reported severe pain, with a mean score of 7/10 on the Numeric Pain Rating Scale and 6/10 on the Douleur Neuropathique 4 Questions (DN4) scale. After one month of topical therapy, pain intensity decreased to mild levels, and the mean DN4 score was reduced to 3/10. Among patients receiving ongoing chemotherapy, clinical improvement was observed without the need to modify treatment regimens or dosages. Importantly, no systemic adverse effects typically associated with oral amitriptyline were reported. These findings indicate that 10% topical amitriptyline provides analgesia primarily through local mechanisms rather than systemic effects, resulting in an improved safety profile compared with oral or parenteral administration and supporting its potential utility in the management of severe CIPN [32].

Preclinical studies conducted by the same authors in murine models demonstrated that topically applied amitriptyline inhibits nociceptor firing, with the strongest inhibitory effects observed for Nav1.8, Nav1.7, and Nav1.9 sodium channel isoforms. Additionally, amitriptyline was shown to induce calcium ion mobilization through activation of transient receptor potential ankyrin 1 (TRPA1) channels. These findings suggest that TRP channels and sodium channels represent important pharmacological targets in neuropathic pain; however, further research is needed in this area [32].

Furthermore, a study by Shakshuki *et al*. demonstrated that the therapeutic efficacy of compounded topical amitriptyline in neuropathic pain depends on its diffusion from the formulation base and penetration through the skin. The diffusion properties of amitriptyline from various compounding bases – including Lipoderm®, Emollient Cream, and Mediflo® 30 Pluronic Lecithin Organogel – as well as factors enhancing skin absorption, are critical for optimal drug release, transdermal penetration, and potentially improved clinical efficacy [34].

4. Capsaicin

Capsaicin is an alkamide naturally occurring in the fruits of plants from the *Capsicum* genus. It has been extensively studied in the field of nociception and pain, although increasing evidence also suggests its potential role in the treatment of other pathological conditions, including cardiovascular diseases, dermatological disorders, malignant tumors, and obesity [35].

The transient receptor potential vanilloid type 1 (TRPV1) channel is the primary receptor for capsaicin and is expressed on central and peripheral terminals of primary sensory neurons. The mechanism of action of capsaicin is based on TRPV1 activation, which leads to a massive intracellular influx of calcium and chloride ions, resulting in prolonged analgesic effects. Capsaicin induces a threefold increase in the permeability of TRPV1-associated ion channels to Ca^{2+}. The influx of calcium ions, together with calcium released from the endoplasmic reticulum, activates intracellular proteases, causing damage to mitochondria and cytoskeletal structures. This process results in functional desensitization of overactivated TRPV1 receptors or temporary degeneration of peripheral nociceptive nerve endings [17,36,37]. Importantly, capsaicin improves neuropathic pain without affecting motor fibers or large sensory nerve fibers responsible for normal sensation [36].

An 8% capsaicin patch is an approved medicinal product for the treatment of neuropathic pain in the European Union and the United Kingdom [38]. Adverse effects are typically limited to the period of patch application and are transient, most commonly presenting as intense burning pain at the application site. Therefore, pretreatment with a local anesthetic, such as EMLA cream, is recommended [17,38].

A single application of an 8% capsaicin patch in patients with localized neuropathic pain provides significant pain relief within 1-2 weeks. This effect results from defunctionalization and temporary degeneration of nociceptive nerve endings in the treated area. Pain symptoms may recur after approximately three months as nerve fibers regenerate, at which point the treatment can be repeated. Blood pressure monitoring during the procedure is recommended. Due to safety requirements – including the use of protective masks, goggles, and nitrile gloves – the treatment should be performed exclusively in specialized pain management clinics [17].

Clinical studies have confirmed the safety and efficacy of capsaicin in the treatment of neuropathic pain, including chemotherapy-induced peripheral neuropathy. Moreover, emerging evidence suggests that topical treatment with an 8% capsaicin patch may exert disease-modifying effects by promoting regeneration and reconstruction of intraepidermal nerve fibers in patients with CIPN [17,38].

5. Cannabinoids

Cannabis has been known to humanity for centuries due to its versatile properties and wide range of applications, including the production of paper, textiles, cosmetics, and food, as well as recreational use and therapeutic applications in medicine, such as epilepsy treatment and pain management [39]. Over the past three decades, significant advances have been made in understanding cannabis-derived compounds and the mechanisms of the endocannabinoid system.

The endocannabinoid system consists of cannabinoid receptors – primarily CB1 and CB2 [39,40], as well as transient receptor potential vanilloid 1 (TRPV1) and other G protein-coupled receptors [41] – endogenous ligands such as anandamide and 2-arachidonoylglycerol (2-AG) [39-41], and enzymes responsible for the synthesis and degradation of these ligands [41]. This system is widely distributed throughout the body and plays a key role in maintaining physiological homeostasis [39]. Exogenous cannabinoids derived from plants (phytocannabinoids) have been shown to interact with the endocannabinoid system, thereby exhibiting potential therapeutic effects [39].

Numerous phytocannabinoids – including cannabidiol (CBD), Δ^9-tetrahydrocannabinol (THC), cannabichromene,

cannabigerol, and others – as well as terpenoids such as β-caryophyllene and limonene have been identified in cannabis plants. Among these compounds, THC and CBD are the most extensively studied [39,40].

Growing evidence suggests that cannabis-based therapies may alleviate symptoms associated with chemotherapy-induced peripheral neuropathy [40-43]. The analgesic effects of cannabinoids are mediated through multiple mechanisms, including inhibition of calcium channel activity, modulation of transient receptor potential (TRP) channels, serotonergic signaling, γ-aminobutyric acid (GABA) and glutamate neurotransmission, as well as immunomodulatory and anti-inflammatory effects [40,41]. However, the use of oral THC- and CBD-based preparations is limited by the relatively frequent occurrence of adverse effects [44]. Studies employing cannabinoid formulations with varying THC-to-CBD ratios indicate that THC is primarily responsible for most adverse effects [42].

THC acts predominantly as an agonist of CB1 [39,40] and CB2 [40] receptors, accounting for its psychoactive and intoxicating properties. In contrast, CBD exhibits minimal psychoactive effects, likely due to its low agonistic activity at CB1 receptors [39,40]. Moreover, CBD has been shown to mitigate undesirable effects associated with THC use, such as anxiety, cognitive impairment, and paranoia [40].

Clinical and experimental studies support the efficacy of transdermally administered cannabinoid-containing preparations in the treatment of neuropathic pain [41,45]. Case reports describe patients with CIPN who experienced pain relief as early as 10-15 minutes after topical application of cannabis-based creams, with analgesic effects lasting from several hours up to 24 hours [40]. Increasingly promising research continues to explore the therapeutic potential of cannabinoids in chemotherapy-induced neuropathic pain, including compounds that lack psychoactive properties [41]. Furthermore, some studies suggest that cannabis-derived compounds may not only alleviate painful symptoms of CIPN but also exert preventive effects against its development [46].

6. Duloxetine

Duloxetine is a selective serotonin-norepinephrine reuptake inhibitor (SNRI) [47-49]. Serotonin and norepinephrine inhibit the transmission of peripheral nociceptive stimuli to neurons of the dorsal horn of the spinal cord [48]. By synergistically enhancing serotonergic and noradrenergic signaling within the synaptic cleft, duloxetine exerts analgesic effects [47-49]. The mechanism of pain inhibition is believed to involve blockade of serotonin and norepinephrine transporters, inhibition of sodium channel currents, and modulation of neural networks responsible for pain suppression [50].

Duloxetine is currently the only agent with proven efficacy in the treatment of pain associated with chemotherapy-induced peripheral neuropathy and has been approved as a first-line pharmacological option [51]. Preparations containing duloxetine are the only drugs recommended in international guidelines for the management of CIPN [9,52-54]. In phase II and III clinical trials [55,56], duloxetine demonstrated clear effectiveness in reducing neuropathic symptoms following chemotherapy [48,50,54].

However, oral duloxetine therapy is associated with a number of potentially serious adverse effects, including hepatotoxicity, renal dysfunction, weight gain, anorexia, fatigue, and xerostomia [47]. Additionally, its oral administration is characterized by limited bioavailability due to extensive first-pass hepatic metabolism [57]. For this reason, research efforts have focused on the development of transdermal formulations to minimize systemic side effects. Experimental studies in rats have shown that a gel containing duloxetine hydrochloride, enriched with methylcobalamin and geranium oil, is effective in alleviating pain associated with chemotherapy-induced neuropathy [47].

7. Ketamine

Ketamine is a non-competitive antagonist of the N-methyl-D-aspartate receptor (NMDAR) and is widely known as a dissociative anesthetic and analgesic derived from phencyclidine. Its primary effect is exerted through anesthesia of the central nervous system [58]. Although ketamine is most commonly administered intravenously, it has also been explored as a topical agent in the treatment of neuropathic pain.

The local analgesic action of ketamine is attributed mainly to blockade of peripheral NMDARs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), and metabotropic glutamate receptors, as well as inhibition of glutamate release [17]. Furthermore, ketamine has been shown to inhibit the development and reduce the severity of neuropathic pain by suppressing inflammatory signaling pathways in specific types of glial cells, which play a key role in pain sensitization [59]. Evidence suggests that ketamine may not only alleviate pain symptoms but also interfere with the initiation and progression of neuropathic pain at its source [60].

In animal models of chemotherapy-induced neuropathy, particularly paclitaxel-induced neuropathy, ketamine has demonstrated analgesic efficacy. In a rat study, systemic administration of ketamine reduced mechanical allodynia and thermal hyperalgesia. Notably, higher doses were required to achieve a significant reduction in pain thresholds in male rats compared to females [61].

As with many other agents, topical administration of ketamine offers the advantage of maintaining low systemic plasma concentrations, thereby minimizing adverse effects. NMDARs are present not only in the central nervous system but also within peripheral nerve axons. In neuropathic and inflammatory pain states, locally applied ketamine reduces pain by downregulating increased expression of NMDA, AMPA, and kinin receptors. Clinical observations indicate that topical creams containing ketamine at concentrations of up to 10%, either alone or in combination with other analgesics, can effectively reduce neuropathic pain, tactile allodynia, and Visual Analog Scale scores within approximately 30 minutes of application [59].

Despite these promising findings, the evidence remains inconsistent. Some studies have failed to demonstrate efficacy of topical ketamine formulations. In a large phase III randomized, placebo-controlled trial involving 462 patients, Gewandter *et al*. reported that a topical cream containing 2% ketamine and 4% amitriptyline did not significantly reduce

CIPN symptoms in cancer survivors [62]. Nevertheless, other studies have consistently shown that topical ketamine is associated with a minimal side-effect profile. Therefore, although the evidence supporting topical ketamine use is weaker than that for other administration routes, it may still be considered in selected patients due to its favorable safety profile [59].

8. Baclofen

Baclofen is an agonist of the gamma-aminobutyric acid type B (GABA) receptor. It exerts an inhibitory effect on synaptic transmission by increasing intracellular potassium ion (K^+) influx and reducing calcium ion (Ca^{2+}) influx [63]. GABA receptors are widely distributed throughout the central nervous system. At the level of the spinal cord, activation of these receptors leads to hyperpolarization of afferent fibers and inhibition of mono- and polysynaptic transmission.

GABA receptors are also expressed in the skin, particularly on C-fiber nerve endings and keratinocytes. Although the exact mechanism of local baclofen action has not been fully elucidated, it is presumed to involve modulation of potassium channels and attenuation of local inflammatory processes [63,64].

In topical therapy, baclofen is primarily used as a component of compounded formulations. In one study, a response test was performed using various compounded pain creams containing combinations of 10% amitriptyline, 10% ketamine, 5% baclofen, 0.2% clonidine, and 10% phenytoin in patients with neuropathic pain of different etiologies, including CIPN. These preparations produced a rapid analgesic response within minutes, resulting in at least a 2-point reduction on the Numerical Rating Scale and a pain reduction of 50% or greater during chronic use. Treatment efficacy was defined as a minimum 2-point difference in pain reduction between the active and placebo creams within 15-30 minutes after application [65].

Barton *et al*. conducted a randomized controlled trial evaluating the efficacy of a topical compounded formulation containing amitriptyline, ketamine, and baclofen in patients with CIPN. The study included 208 participants who applied the compound twice daily for four weeks. The formulation consisted of baclofen (10 mg), amitriptyline hydrochloride (40 mg; 3%), and ketamine (20 mg; 1.5%) in a pluronic lecithin organogel base. Compared with placebo, patients receiving the active compound experienced significant improvement in sensory and motor symptoms, including reductions in tingling, cramps, stabbing or burning pain, and functional difficulties such as impaired fine motor skills. No adverse effects were reported [66].

Despite these findings, the American Society of Clinical Oncology guidelines for the prevention and treatment of CIPN do not currently recommend the use of topical compounded preparations containing baclofen, amitriptyline, with or without ketamine, due to limited evidence and a lack of recent high-quality studies. Further research is necessary to confirm the efficacy and safety of these topical combinations in patients with CIPN [53].

Table 1. Mechanism of drug action in CIPN

Medicine	Mechanism of drug action in CIPN
Phenytoin	• Blockade of voltage-gated sodium channels (Nav) • Immunomodulatory effects contributing to the regulation of peripheral inflammatory processes in small epidermal nerve fibers, resulting in reduced hyperexcitability of nociceptive nerve endings
Lidocaine	• Blockade of pathological voltage-gated sodium channels (Nav) involved in ectopic discharges • Inhibition of the release of pronociceptive mediators from keratinocytes
Amitriptyline	• Inhibition of monoamine (serotonin and norepinephrine) reuptake • Blockade of voltage-gated sodium channels • Anticholinergic effects via muscarinic receptor antagonism and antihistaminic activity
Capsaicin	• Activation of transient receptor potential vanilloid 1 (TRPV1) channels, resulting in a massive intracellular influx of calcium and chloride ions and subsequent functional desensitization of nociceptive fibers
Cannabinoids	• Inhibition of calcium channel activity and transient receptor potential (TRP) channels • Modulation of serotonin, γ-aminobutyric acid (GABA), and glutamate receptor signaling • Immunomodulatory and anti-inflammatory effects
Duloxetine	• Inhibition of serotonin and norepinephrine transporters • Blockade of sodium channel currents • Modulation of descending inhibitory pain pathways
Ketamine	• Non-competitive antagonism of peripheral N-methyl-D-aspartate receptors (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), and metabotropic glutamate receptors (mGluR) • Inhibition of glutamate release
Baclofen	• γ-aminobutyric acid type B (GABA_B) receptor agonism • Inhibition of synaptic transmission through increased intracellular potassium (K^+) influx and reduced calcium (Ca^{2+}) influx

DISCUSSION

This narrative review provides a comprehensive analysis of topical treatment options for chemotherapy-induced peripheral neuropathy (CIPN), focusing on agents that are not conventionally associated with standard CIPN management. The findings highlight the potential of topical therapies to provide meaningful symptomatic relief while improving patients' quality of life (QoL). This section discusses the key observations of the review, the limitations of the available evidence, methodological constraints, and the implications for clinical practice, health policy, and future research.

The favorable outcomes reported for topical agents such as phenytoin, lidocaine, amitriptyline, capsaicin, cannabinoids, duloxetine, ketamine, and baclofen are consistent with the growing body of literature exploring alternatives to systemic pharmacotherapy. These findings complement existing studies by elucidating possible mechanisms of action and emphasizing the advantages of local drug delivery compared with systemic administration, particularly with regard to reducing systemic adverse effects and improving treatment adherence.

Nevertheless, the evidence supporting the efficacy of topical treatments for CIPN remains limited. Many of the studies included in this review were characterized by small sample sizes, short follow-up periods, or the absence of placebo-controlled designs, which may introduce bias and limit the strength of the conclusions. In addition, substantial heterogeneity in study designs, patient populations, outcome measures, and chemotherapy regimens complicates the generalizability of the results. Variability in drug concentrations, formulations, and application protocols further limits direct comparisons of efficacy between individual topical agents.

Despite these limitations, the findings of this review have important implications for clinical practice. Topical

treatments may be considered as part of a multimodal approach to CIPN management, particularly in patients who are intolerant of, or unresponsive to, conventional systemic therapies. From a policy perspective, there is a clear need for evidence-based guidelines to standardize the use of topical agents, ensuring their safety, efficacy, and accessibility. Future research should prioritize large, well-designed randomized controlled trials to evaluate the long-term benefits and potential risks of topical treatments for CIPN. Emphasis should also be placed on patient-centered outcomes, including QoL, functional status, and daily activity performance. Furthermore, the development of innovative drug delivery systems capable of enhancing skin penetration and therapeutic efficacy warrants continued investigation.

CONCLUSIONS

Chemotherapy-induced peripheral neuropathy affects an increasing number of patients, underscoring the need for the development of novel and effective treatment strategies. In this review, we focused on topical agents that are not traditionally associated with CIPN therapy but may offer clinically meaningful pain relief when adequately investigated. The available evidence supports the potential effectiveness of topical phenytoin, lidocaine, amitriptyline, capsaicin, cannabinoids, duloxetine, and ketamine in the management of CIPN-related pain.

In addition, emerging data suggest that capsaicin may promote regeneration and repair of intraepidermal nerve fibers, while cannabinoids may have a role not only in symptom control but also in the prevention of CIPN. Ketamine has been proposed as a potential agent capable of limiting the development and progression of neuropathic pain at its source. In contrast, evidence supporting the use of topical baclofen in CIPN remains limited and requires further investigation.

The use of topical agents may allow for a reduction in oral analgesic doses and may be preferred over systemic therapies due to their favorable safety profile. Greater emphasis should therefore be placed on topical treatments as promising therapeutic targets aimed at minimizing systemic adverse effects and optimizing current pharmacotherapy, ultimately improving outcomes for patients with CIPN.

ORCID iDs

Karolina Pawelec https://orcid.org/0009-0000-0543-9395
Sabina Jóźwiak https://orcid.org/0009-0004-5262-9967
Karolina Iwanicka https://orcid.org/0000-0002-8803-332X
Ewelina Wesołek-Bielaska https://orcid.org/0000-0001-7819-2661
Katarzyna Szklener https://orcid.org/0000-0001-8033-3574
Sławomir Mandziuk https://orcid.org/0000-0002-9812-0777

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