Neoplasma 2022; 70(1): 15–35

doi:10.4149/neo_2022_221007N992

Prevention and therapy of chemotherapy-induced peripheral neuropathy: a review of recent findings

Minireview

Zuzana MICHALOVÁ*, Eva SZÉKIOVÁ, Juraj BLAŠKO, Ivo VANICKÝ

Institute of Neurobiology, Biomedical Research Center, Slovak Academy of Sciences, Košice, Slovakia

**Correspondence: michalova@saske.sk*

Received October 7, 2022 / Accepted November 13, 2022

Chemotherapy-induced peripheral neuropathy is one of the most frequent dose-limiting side effects, observed in patients receiving antineoplastic agents, persisting for up to two years after completing treatment, greatly affecting both the course of chemotherapy and patients' quality of life. Approximately 20 to 85% of patients treated with neurotoxic chemotherapy will develop peripheral neuropathy and there is considerable variability in its severity among patients. The main symptoms are numbness, paresthesia, and burning pain in a "glove and stocking" distribution. The prevalence of chemotherapy-induced peripheral neuropathy will likely increase as cancer survival rates continue to improve. Currently, there are only a few therapeutic options available for the prevention or successful therapy because the mechanisms of chemotherapy-induced peripheral neuropathy remain unclear. A better understanding of the risk factors and underlying mechanisms of chemotherapy-induced peripheral neuropathy is needed to develop effective preventive and therapeutic strategies.

Key words: cancer; peripheral neuropathy; prevention; therapy; antineoplastic agents

Chemotherapy-induced peripheral neuropathy (CIPN) is generally classified as a series of neuromuscular symptoms, both sensory and motor, that result from peripheral nerve damage caused by exposure to a neurotoxic chemotherapeutic agent, including taxanes, platinum compounds, vinca alkaloids, and others (Table 1). The exact incidence and prevalence of CIPN vary between chemotherapeutic drugs, their combinations, and studies. It is estimated that at least 20% of patients receiving neurotoxic antineoplastic drugs will develop some degree of CIPN. The characteristics of CIPN depend on the particular chemotherapeutic drug used, as well as the amount of dose [1]. Symptoms may be mild or severe, acute, transient, or chronic, and there is considerable variability in their severity among patients depending on the drug regime and dose of the drugs [1, 2]. In clinical practice, the recognition of this heterogeneous symptomology relies mainly on the results reported by patients, which are supported by clinical examination and neurophysiological studies [3]. The exact cause of CIPN still remains unclear despite great progress in the characterization of CIPN. Various preclinical studies have suggested the possible involvement of oxidative stress, humoral factors, ion channels and receptors, as well as infiltrating macrophages in the development or maintenance of CIPN [4]. Unfortunately, to date, there is only minimal evidence of the efficacy of substances that would appear to be effective in prevention, as well as in the treatment of CIPN [5]. Preventive and therapeutic approaches remain extremely limited, mostly with inconsistent results, and require further study. None of the known therapies will reverse neuropathy, although some substances can effectively alleviate pain. In this review, we provide an overview of the results of studies on current clinical models of peripheral neuropathy and ongoing research to better understand CIPN and develop potential treatment options.

Clinical features

In some patients, CIPN symptoms may occur gradually over a prolonged period, but it is not uncommon that symptoms to appear suddenly and intensely [2]. Patients affected by CIPN clinically present a variable involvement of sensory, motor, and autonomic function. Sensory

Table 1. Chemotherapeutic agents associated with peripheral neuropathies.

Class	Agent	Mechanism of action	Incidence of CIPN (%)	Mechanism of CIPN	Symptoms	Ref.
Platinum compounds	Cisplatin	alkylation of DNA	14–63	inflammation, ROS production, mitochondrial dysfunction, protease activation	predominantly sensory neuropathy, painful paresthesia, numbness, tingling, impaired vibration sense	[141–143]
	Oxaliplatin	alkylation of DNA	18–100	altered ion channels, mitochondrial dysfunction, loss of sensory neurons, ROS production	acute sensory symptoms and chronic sensory neuropathy, acute cold-induced paresthesia, cramps, numbness, functional disability	[179–181]
	Carboplatin	alkylation of DNA	4–6	ROS production, mitochondrial dysfunction	numbness, tingling, weakness, and tremor, gait ataxia	[182, 183]
Taxanes	Paclitaxel	microtubule stabilizer	20–50	microtubule impairment, loss of axon transport function, inflammation, ROS production, mitochondrial dysfunction	predominantly sensory neuropathy, painful paresthesia, numbness, decreased vibration or proprioception	[15, 25, 184]
	Docetaxel	microtubule stabilizer	11–64	microtubule impairment, loss of axon transport function, inflammation, ROS production, mitochondrial dysfunction	predominantly sensory neuropathy, painful paresthesia, numbness	[185, 186]
	Cabazitaxel	microtubule stabilizer	5–8	microtubule impairment, loss of axon transport function	predominantly sensory neuropathy, numbness	[187]
Vinca alkaloid	Vincristine	prevention microtubule polymerization	35–45	microtubule impairment, loss of axon transport function, altered ion channels, neuroinflammation	sensory neuropathy, hypoesthesia, tingling paresthesia, muscle cramps, autonomic neuropathy	[188]
Immunomodulatory drug	Thalidomide	immunomodulatory effect	≤83	ROS production	sensory neuropathy, muscle cramps, and mild distal weakness	[28, 41]
Proteasome inhibitor	Bortezomib	proteasome 26S inhibitor	≤50	increased sphingolipid metabolism, inflammation, mitochondrial damage, ROS production	painful, small-fiber sensory neuropathy, autonomic neuropathy painful paresthesia, burning sensation	[22, 28]
Halichondrin B analog	Eribulin	microtubule inhibitor	≤28	microtubule impairment	the lowest incidence of severe neuropathy	[189–191]

symptoms may include sharp pain or numbness, pins and needles sensation, hyperalgesia, tingling, burning, ataxia, loss of deep tendon reflex, loss of proprioception sense, and a reduced sense of touch and vibration. The development of the symptomatology follows a "glove and stocking" distribution, respectively, due to the vulnerability of the long nerves. Motor symptoms may include itching, muscle cramps and muscle weakness, thinning of muscles, balance disturbances, and difficulty performing fine motor skills. However, motor symptoms are considerably less frequent because of the inability of the neurotoxic agents to cross the blood-brain barrier in concentrations responsible for harm [1, 2]. The autonomic system may also be affected, resulting in nausea and vomiting after eating, diarrhea, constipation, urinary retention, sexual dysfunction, or altered blood pressure [2, 6]. It is very common that CIPN symptoms intensify after the neurotoxic agent has been discontinued. This is known as the coasting effect, and it is the result of the accumulation of the neurotoxic agent within the body. All these CIPN symptoms negatively alter a patient's ability to perform common activities, such as sleeping, driving, standing, exercising, walking, or cooking [7, 8].

Prevalence and risk factors

In general, the prevalence and incidence of CIPN vary depending on the chemotherapeutic drug used, the dose, the duration of treatment, and the route of administration [1]. Most studies report that more than 60% of patients are affected in the first month after stopping treatment. However, in many patients, CIPN symptoms persist for more than 6 months after cessation of therapy [9], even in some cases, such as oxaliplatin treatment in colorectal cancer patients, 42% to 84% of patients had CIPN symptoms 2 years after treatment [10]. In addition, there are studies examining breast cancer patients who persist with CIPN-related symptoms 1 to 3 years after chemotherapy [11]. Although the overall severity of neuropathy symptoms decreases and sensory nerve conduction improves over time, recovery is often protracted and incomplete.

A number of risk factors involved in an increased risk of developing CIPN have been identified, although causal associations are less clear. Several specific diseases are considered to be serious risk factors for peripheral neuropathy. Examples include diabetes, hypothyroidism, renal insuffi-

ciency, and also pre-existing neuropathy. In addition, there are numerous other factors contributing to the individual risk of CIPN, such as alcohol misuse, vitamin deficiencies, raised body mass index (BMI), smoking, infections, autoimmune diseases, such as rheumatoid arthritis or lupus, and family history of neuropathy [12]. Some of the studies on animal rodent models have focused on the prevalence of genetic risk factors in CIPN development [13, 14]. The authors suggest that polymorphisms of crucial enzymes and transporters, important for pharmacologic processes of chemotherapeutics, such as glutathione transferases, ATP binding cassette transporters, cytochrome P450 enzymes and others, may explain the fundamental basis of CIPN and may be involved in the development of various symptoms of CIPN [15–17]. As noted above, all of these genetic risk factors may affect the absorption and metabolism of some chemotherapeutic agents, which could be related to the formation of CIPN. The studies with risk factors and genetic polymorphisms associated with CIPN are discussed and summarized in Table 2.

Pathophysiology

The pathophysiology of CIPN has been analyzed by various studies and reviews [18–21]. Although the exact mechanism is still not fully understood, the underlying mechanisms of CIPN are considered to be multifactorial with different points of involvement. Neurotoxicity of different chemotherapeutic drugs is mediated by interference with a variety of molecules and cellular structures. Chemotherapeutic drugs exert their neurotoxic effects on sensory cell bodies in the dorsal root ganglia (DRG), which is called neuronopathy, on myelin sheets, causing myelinopathy, and on axonal components, resulting in axonopathy. Other possible mechanisms include ion channels' dysfunctions, destruction of the microtubules, mitochondrial damage, and damage of the surrounding blood vessels [22–25]. While some of the neurotoxic mechanisms have been known for a long time and have been extensively studied, other entities such as immunological processes and neuroinflammation have been recently discovered.

The sensory cell bodies in the DRG are a vulnerable structure because they are located outside the protective blood-nerve barrier and thus easily come into contact with various neurotoxic drugs, such as chemotherapeutic agents [26]. DRGs are responsible for transmitting afferent signals through sensory nerve fibers to the posterior grey column [27], so a possible explanation for the prevailing CIPN sensory symptoms may be damage to the DRG. Neurotoxic mechanisms of platinum derivates, taxanes, vinca alkaloids, thalidomides, and bortezomib are involved in DRG damage.

Other drugs, such as bortezomib, affect the myelin layer and cause demyelinating damage [28]. The myelin layer enables saltatory conduction [27], the damage of which

Table 2. Some of the risk factors and genetic polymorphisms associated with an increased risk of CIPN.

		Comments:	Ref.
Risk factors associated with CIPN	older age	lower chance to recover after CIPN	[1, 9, 192]
	comorbid health conditions	e.g., diabetes, HIV, decreased creatinine clearance, thermal hyperalgesia	[9, 193, 194]
	estrogen decline	estrogen protects against CIPN development	[192]
	tobacco use	long-term heavy smoking reduces peripheral blood flow, likely exacerbating PIN	[193]
	preexisting neuropathy	increases the risk of serious symptoms	[195]
	raised BMI	related to the pro-inflammatory state associated with obesity	[1, 9]
	low serum albumin	reflects the lower general health status	[1, 9]
	NfL in plasma or serum samples	neuroaxonal damage in peripheral nerves results in the release of NfL into the extracellular space and peripheral blood	[77, 196]
	hypertension	microvascular complications associated with hypertension may contribute to CIPN	[197]
	use of beta-blockers	opportunity to modify the effect of medication	[198]
Genetic polymorphisms associated with CIPN	GSTP1	associates with a decreased risk of OIN	[15, 199, 200]
	CYP2C8	associates with decreased metabolism of paclitaxel and thus increase the risk of developing neuropathy	[17, 201]
	OCT2	knockout of OCT2 prevents the development of cold and mechanical hypersensitivity following oxaliplatin therapy	[202, 203]
	ABCC2	associates with OIN	[200, 204]
	AGXT	correlated with the severity of CIPN in patients on oxaliplatin therapy	[17]
	SCN4A	associates with an increased incidence of acute OIN	[205]
	SCN10A	associates with an increased incidence of acute OIN	[205]
	SCN9A	protects against severe OIN	[206, 207]

Abbreviations: PIN-paclitaxel-induced neuropathy; OIN-oxaliplatin-induced neuropathy; NfL-Neurofilament light chain; GSTP1-glutathione S-transferase P1; OCT2-organic cation transporter 2; ABCC2-ATP binding cassette subfamily C member 2; AGXT-alanine glyoxylate aminotransferase; SCN4A-sodium channel protein type 4 subunit alpha; SCN10A-sodium channel protein type 10 subunit alpha; SCN9A-sodium channel protein type 9 subunit alpha

consequently causes a painful, reversible, length-dependent small fiber axonal sensory neuropathy and impairs the transmission of electrical stimuli [22].

Another possible mechanism is direct axonal toxicity [29]. Platinum derivatives impair the function of the ion channels, which inhibits the transmission of electrical stimuli and information in the synaptic cleft [30–32]. Conversely, this damage can also lead to peripheral nerve hyperexcitability [33].

Some neurotoxic chemotherapeutics damage the microtubules that supply the axons, causing them to degenerate gradually [34–36]. Microtubules are responsible for substance transport within the nerve cell, and drugs such as taxanes, vinca alkaloids, and also bortezomib that destroy the microtubules, lead to restrictions in the axonal transport processes as well as the energy supply. Restriction in energy supply leads ultimately to cell death [23].

Chemotherapy drugs also exert their toxicity on mitochondria, which are the major source of reactive oxygen species (ROS). Mitochondrial dysfunction leads to increased generation of ROS and, consequently, to the generation of oxidative stress. Gamper and Ooi reviewed the evidence for ROS and reactive nitrogen species (RNS) involvement in neuropathic pain and their multiple effects on neuronal excitability [37]. Recent studies have measured ROS and RNS concentrations using *in vivo* CIPN models to understand the cellular location of oxidative stress during CIPN. Increased RNS levels were indicated in the spinal cord of paclitaxel-treated rats [38], and increased ROS and RNS concentrations were also seen in lumbar DRG after oxaliplatin treatment [39]. Paclitaxel is associated with structural change processes in the axonal mitochondria [40].

Damage to the surrounding blood vessels by thalidomide leads to restricted substances transport and thus to an undersupply of the axons [41]. Impaired angiogenesis due to its antiangiogenic effects is considered to be a significant factor influencing the development of CIPN [24].

A recent new animal model study suggests that the neurotoxicity of paclitaxel may depend on interactions between cutaneous nerve endings and epidermal basal keratinocytes via the matrix metalloproteinase 13 (MMP-13) [25]. Excessive MMP-13 activity may lead to increased collagen degradation, which could alter the mechanical properties of the skin, given the collagen-rich network within the extracellular matrix that is essential to maintain tissue integrity [42]. Skin disruptions due to increased MMP-13 activity may promote axon degeneration.

Chemotherapy agents also engage the innate immune system to induce peripheral neuropathy. Activation of key mediators, the toll-like receptors (TLRs) by chemotherapeutics increases pro-inflammatory cytokine expression in the peripheral and central nervous systems. TLR4 and its immediate downstream signals are increased in the rats' DRG with paclitaxel-induced hyperalgesia [43]. Paclitaxel-induced increased signaling of TLR4 in DRG neurons leads to increased expression of C-C chemokine ligand 2 (CCL2) [44]. CCL2 and its receptor, C-C chemokine receptor 2 (CCR2), are key players in the attraction of monocytes to sites of injury and inflammation [45], leading to increased concentrations of Interleukin-1 (IL-1) and Tumor necrosis factor alpha (TNFα) in the DRG. These pro-inflammatory cytokines produce hyperalgesia to thermal and mechanical stimuli [46, 47], lower spinal and DRG neurons' threshold of activation, induce spontaneous discharges [48, 49], and also increase the release of bradykinin, serotonin, and histamine that further augment pro-inflammatory processes [50]. Moreover, TNFα also specifically suppresses the signaling of spinal GABA neurons, leading to central disinhibition of pain signaling [51].

Unlike traditional chemotherapy, a promising new class of anticancer drugs specifically targets the immune response instead of cancer cells. Immune checkpoint inhibitors (ICIs) play an important role in downregulating the immune response and modulating its intensity [52, 53]. Specifically, ICIs induce increased differentiation of T cells to a Th1/Th17 response, that promotes a pro-inflammatory profile, and reduced production of the Th2 cytokines IL-5 and IL-13 [54, 55]. Potential cross-reactivity between tumor neo-antigens and self-antigens is probably responsible for immunotherapy-related neurological complications [56]. Especially the direct binding of ICIs to antigens expressed in normal tissue seems to induce antibody-dependent toxicity and complement-mediated inflammation [57].

Subsequently, common degenerative pathways leading to the activation of apoptotic signaling cascades and alteration of neuronal excitability are triggered, which may in turn lead to epidermal fiber loss [58]. In addition to changes in peripheral neurons, long-term changes in the central nervous system can result in chronic pain, characteristic of CIPN [20]. Regardless of which of the possible underlying mechanisms is involved in the pathophysiology of CIPN, these stimuli lead to impaired communication between the peripheral and central nervous systems, causing the above symptoms and functional changes.

Assessment and diagnosis of CIPN

There is currently no widely standardized assessment approach for the diagnosis of CIPN; however, the number of diagnostic guidelines for neuropathic pain, in general, may be also useful in CIPN. As some chemotherapeutic drugs may induce polyneuropathy-like symptoms, differential diagnoses should be considered to ensure appropriate treatment of patients with CIPN [1]. CIPN must be differentiated from other types of neurosensory manifestations such as toxic, diabetic, or paraneoplastic sensory neuropathy. Due to the complex nature of the pathogenesis and the resulting clinical manifestation of CIPN, the diagnosis is very complex. Hundreds of different diagnostic approaches have recently been identified in the literature

that differ in patient validity, sensitivity, and compliance of the patients [59]. International guidelines recommend the use of screening questionnaires to identify potential patients. However, clinical examination is also an important and useful tool of assessment. These guidelines also recommend neurological examination of cancer patients prior to potentially neurotoxic cancer therapies in order to identify high-risk patients [5]. Patients with pre-existing peripheral nervous system dysfunctions are predisposed to the formation of CIPN [21]. Once CIPN is suspected in predisposed patients, further diagnosis is made based on anamnesis, patients' documentation of neurotoxic complaints, and clinical presentation [60]. Quantitative sensory testing (QST) in clinical routine is a feasible tool to evaluate CIPN amongst cancer patients and may have clinical utility in the early assessment of CIPN [61]. Impaired thermal sense is best assessed with warm and cold objects, tactile senses with a cotton swab or wooden stick, and vibration sense with a tuning fork [62]. Other screening tools include painDETECT®, which contains nine sensory symptom items and was designed to detect and document pain in clinical practice [63], or DN4 (Neuropathic Pain in 4 Questions), which includes patient questions as well as items based on clinical examination [64]. The FACT/GOG-Ntx and European Organisation for the Research and Treatment of Cancer Quality of Life (EORTC QLQ-CIPN20) questionnaires are the most commonly used [65, 66]. The questionnaires measure the subjectively perceived impact of CIPN symptoms on patients' daily lives and their health-related quality of life over 7 days. EORTC QLQ-CIPN20 contains 20 items divided into three subgroups assessing sensory, motor, and autonomic symptoms. Each item is scored on a Likert scale ranging from 1 (which means not at all) to 4 (which means very much). After that, the score is transformed to a 0–100 scale, with higher scores representing more complaints. The reduced version of CIPN20 – CIPN15 provides a shortened length of the questionnaire without affecting its reliability. It no longer includes hearing loss, use of car pedals and 3 autonomous items, as well as CIPN16, which also excludes questions about autonomic symptoms and hearing loss [67, 68]. The Treatment-induced Neuropathy Assessment Scale (TNAS) is a 13-item rating scale based on a 0–10 rating system. The TNAS examines difficulty with walking and strength, as well as the occurrence of sensory symptoms [69]. Patient reporting of CIPN symptoms has also been recorded through electronic platforms such as the Neuropathy Screening Question (NSQ), which examines the presence of sensory symptoms recorded in the previous seven days on a scale from 0 to 10. Compared to sensory CIPN20, the NSQ subscale showed sufficient sensitivity and high specificity in detecting CIPN symptoms [70]. In patients with normal or negative results from other diagnostic tools, skin biopsies may be performed to support the diagnosis, as CIPN is also in some patients the result of small nerve fiber dysfunction [71]. In addition, nerve conduction studies (NCSs), electromyography, and quantitative sensory testing may support the clinical evaluation of CIPN [60]. NCSs are considered the most effective non-invasive method for determining the type of neuronal damage [72]. Briefly, the nerve is electrically stimulated percutaneously and the resulting electrical excitation propagation is derived distally from the stimulation site above the innervation area. However, NCSs only reflect neuronal damage of the large myelinated nerve fibers and not the small non-myelinated nerve fibers. If these are affected, the results show normal values [65]. Corneal confocal microscopy (CCM) is a new non-invasive ophthalmic imaging technique that can detect small nerve fibers in the cornea and is used for the diagnosis and prognosis of small nerve fiber loss in patients with diabetes and other neuropathies [73–75]. Chiang et al. studied cancer patients with various etiology receiving paclitaxel or oxaliplatin within the past 3 to 24 months. Their study showed a significant reduction in corneal nerve fiber number and density, as well as corneal nerve fiber lengths in patients with neuropathy compared to patients without neuropathy. Their results suggest that CCM may have diagnostic and prognostic value in CIPN [76]. Moreover, the biochemical analysis could provide a relevant advantage in the clinical management of cancer patients undergoing chemotherapy. Meregalli et al. recently investigated the utility of serum neurofilament light chain (NfL) as a biomarker of CIPN in rats treated with vincristine, cisplatin as well as paclitaxel. The authors described significantly increased serum NfL values during drug administration, up to a 4-fold increase after treatment compared to controls. In particular, an increase in NfL was correlated with axonopathy and intraepidermal nerve fibers (IENF) loss investigated behaviorally, neurophysiologically, and pathologically [77].

The apparent lack of consistency in the assessment of CIPN has implications for imprecise epidemiological studies. This problem has been identified in several systematic reviews, which have simultaneously emphasized the need for more consistent and uniform approaches to assessment and diagnosis to provide a detailed and accurate understanding of CIPN.

Prevention

Several research studies have focused on the investigation of pharmaceutical and non-pharmaceutical preventive measures in prophylactic interventions to prevent CIPN-associated functional loss, so far without satisfactory results. Although a number of preventive therapies and drugs have been tested in the past for potential benefit in CIPN symptoms, many strategies are currently proving ineffective. Such therapies without clinically meaningful benefits include drugs successfully used in other indications, such as acetyl-L-carnitine [78], alpha-lipoic acid [79], pregabalin [80], vitamin E [81], vitamin B [82], calcium and magnesium

[83], and electroacupuncture [84]. Overview of the pharmacological and non-pharmacological preventive options are listed below and summarized in Table 3.

Targeting manganese superoxide dismutase (MnSOD) has proven to be a promising strategy for preventing CIPN symptoms. A mangafodipir derivative, calmangafodipir, is the mitochondrial mimetic MnSOD, which can reduce tissue ROS levels. However, preclinical and clinical CIPN data have confirmed that these compounds have significant neuroprotective and preventive activity. Calmangafodipir was studied in a placebo-controlled clinical trial in patients receiving oxaliplatin-based chemotherapy. The results of this study confirm the protective effect of calmangafodipir against chemotherapeutic-induced small fiber neuropathy [85].

El-Fatatry et al. evaluated metformin as a means of preventing oxaliplatin-induced PN compared to a control group. Metformin is a widely used antidiabetic drug that activates adenosine monophosphate-activated protein kinase. Due to its antioxidant properties, it reduces ROS, nitric oxide, and other markers of oxidative stress. Metformin protects against CIPN due to its neuroprotective effect. The authors reported that at the end of the 12th cycle of chemotherapy, neuropathy was lower in the metformin group compared to the control group. Due to the small sample size, more confirmatory studies are needed before recommending this approach for oxaliplatin-induced PN [86].

Gabapentin and pregabalin are effective in the treatment of many forms of neuropathic pain, but their role in the prevention and treatment of CIPN is not clearly established. A randomized placebo-controlled study of gabapentin has been identified. The rate of grade 2 and 3 neuropathy was significantly lower in the gabapentin group compared to the placebo, suggesting that gabapentin given prophylactically with paclitaxel is effective both objectively and subjectively in moderate and high-grade neuropathies [87].

Dose-adjustment approaches have traditionally been the gold standard for the non-pharmacological management of CIPN symptoms. They can help reduce the severity of CIPN symptoms while maintaining treatment effectiveness [88]. Several clinical trials have focused on dose reductions in patients with neurotoxic symptoms. Beijers et al. have aimed to study the influence of cumulative dose, dose schedule, and dose reductions of adjuvant oxaliplatin on the long-term severity and prevalence of CIPN among colorectal cancer patients. Patients who received a cumulative oxaliplatin dose had a significantly worse sensory score compared to those who received a low cumulative dose [89].

Cooling of hands and feet during chemotherapy administration may prevent some of the CIPN symptoms [89, 90]. Beijers et al. have investigated the efficacy of wearing frozen gloves (FGs) to prevent CIPN. Wearing FGs during treatment might reduce some neuropathy symptoms, mostly in the fingers and hands, potentially resulting in a better patient quality of life [90]. The authors of the study also found that these observations are mainly clinically important in the short term but have no clinical significance in the long term.

Tsuyuki et al. have developed a surgical glove (SG) compression therapy to investigate the efficacy and safety of compression therapy for the prevention of CIPN. Compression with too small SGs significantly reduced the overall incidence of CIPN symptoms by decreasing the micro-

Table 3. Selected agents evaluated for prevention of CIPN.

	Agent	Limitations of Studies/Agents	Ref.
Beneficial	calmangafodipir	recommended in small fiber neuropathy	[85]
	metformin	small trial	[86]
	gabapentin	not specified	[87, 208]
	dose adjustment	not specified	[89]
	frozen gloves	higher price, skin disorders	[90]
	compression therapy	non-randomized study	[91]
	cryo-compression therapy	small trial	[92]
	rTMS	not specified	[96]
	PDD	recommended in oxaliplatin-based chemotherapy	[99]
	henna	not specified	[101]
	functional exercises (mobility, sensorimotor, and vibration training), endurance training	not specified	[93–95]
No proven benefit/ Harmful	acetyl-L-Carnitine	worsen neuropathy	[78]
	alpha-lipoic acid	no statistical difference with the control group, many side effects	[79]
	pregabalin	negative trial	[80]
	vitamin E	no statistical difference with the control group	[81]
	vitamin B	no statistical difference with the control group	[82]
	calcium and magnesium	no statistical difference with the control group	[83]
	electroacupuncture	slower recovery than the control group	[84]

Abbreviations: rTMS-repetitive transcranial magnetic stimulation; PDD-polyamine-deprived diet

vascular flow to each fingertip and reducing each fingertip temperature by 1.6–2.2°C, without any dermatological adverse effects related to the use of SGs [91]. The authors suggest some advantages over the use of frozen gloves with respect to the higher price and variable skin disorders attributed to cryotherapy, such as cold intolerance and cold-related injuries. However, this preventive approach addressed in this study is still considered less effective, probably due to methodological shortcomings in the study design, such as a non-randomized study and the use of subjective methods to assess PN.

Another research group conducted evidence of a concept study in cancer patients receiving taxanes. Both cryotherapy and compression therapy were given to the patients during chemotherapy administration. They revealed the maintenance of motor nerve conduction amplitudes compared to baseline. Compared to patients treated with cryotherapy alone, patients appear to have performed better with combination (cryo-compression) therapy [92].

Another preventive approach that should be considered before initiating a potential neurotoxic anticancer treatment is regular functional exercises (mobility, sensorimotor, and vibration training). Recent studies suggest that physical activity may reduce CIPN symptoms and functional impairment [93, 94]. Balducci et al. have shown that endurance training can prevent the development of CIPN [95].

The use of repetitive transcranial magnetic stimulation (rTMS) in neurological conditions has also been studied. rTMS is a noninvasive multisession treatment that uses magnetic fields to stimulate nerve cells in a specific area of the brain through electromagnetic induction, usually to improve symptoms of bad mood or depression. rTMS has been designed to alter brain activity by introducing small magnetic pulses into the scalp that encourage the brain to change activity. In this study, patients were randomized to be treated by rTMS for 30 min over 10 days in comparison with standard care. The authors of the study examined how rTMS works in improving CIPN in cancer patients. It has been proposed that rTMS is a safe and well-tolerated treatment option that can be also effective for patients suffering from headaches, pain, or other neurological conditions such as CIPN [96].

The non-pharmacological studies also aimed to determine whether specific nutritional therapy can prevent acute CIPN symptoms in patients receiving anticancer treatment. A randomized, controlled, single-blind trial aimed to evaluate the efficacy of a polyamine-deprived diet (PDD) compared with a normal polyamine-containing diet for the prevention of CIPN in patients treated with oxaliplatin-based chemotherapy. PDD containing less than 10 mg/kg polyamines reduces pain hypersensitivity in animals [97]. Polyamines are positive modulators of NR2B-containing N-methyl-D-aspartate (NMDA) receptors involved in central sensitization after peripheral nerve injury [98]. As polyamines as such may play a facilitating role in nociceptive neurotransmission and chronic pain, the main hypothesis of this study was that reduced polyamine intake may improve nociceptive symptoms by reducing NMDA receptor activity and subsequently improve cold pain threshold, neuropathic pain symptoms, and other comorbidities, such as anxiety and depression. A study demonstrated the preventive effect of PDD on CIPN on both acute and chronic symptoms of heat hyperesthesia, especially cold hyperesthesia [99].

Among herbal extracts, henna is used to treat diabetic skin ulcers with a small loss of nerve fibers [100], also commonly found in neuropathies occurring after the administration of anticancer drugs. Arslan et al. investigated the effect of henna on CIPN in women treated with oxaliplatin. Henna was applied topically twice a day to the palms, fingers, and soles, and routine treatment and care were provided to control patients. The results of the study showed that henna application has a beneficial effect on CIPN and could be a promising approach in CIPN management [101].

Future preventive approaches. Numerous literature reports have indicated that activation of the Wallerian-like degeneration pathway driven by sterile alpha and TIR motif-containing protein 1 (SARM1) is responsible for axonopathy in CIPN [102–104]. SARM1 is a central driver of axonal degeneration following chemical, inflammatory, mechanical, or metabolic damage to the axon [105]. Bosanac et al. identified a new series of effective and selective irreversible isothiazole inhibitors of SARM1 enzymatic activity that protected rodents and human axons *in vitro*. In their CIPN mouse model, the irreversible SARM1 inhibitors prevented loss of axonal function and provided partial protection of axonal function assessed by sensory nerve action potential amplitude and mechanical allodynia [106].

In vitro and *in vivo* studies have shown that the tyrosine kinase inhibitors, nilotinib and dasatinib, may offer a potential neuroprotective strategy for paclitaxel- and oxaliplatin-induced PN without negatively affecting their antitumor activity. As new-purpose drugs, nilotinib and dasatinib are currently being tested in an ongoing phase Ib/II trial in patients with stage I–III breast cancer and in an ongoing phase Ib trial in patients with metastatic gastrointestinal cancer [107].

Ganglioside-monosialic acid (GM-1) performs an important function in the processes of neurogenesis, neural development and differentiation, cell recognition, and signal transduction [108]. Su et al. evaluated a placebo-controlled, double-blind trial of intravenous GM-1 administered to prevent taxane-induced PN in breast cancer patients. GM-1 treatment resulted in a statistically significant reduction in the severity and incidence of CIPN after 4 cycles of taxane-containing chemotherapy [109]. GM-1 appears to be well tolerated and does not reduce the anticancer effects of the chemotherapy agent [110]. Despite this very positive report, a confirmatory study is needed to approve these findings and the efficacy of GM-1 in the prevention of peripheral neuropathy induced by different types of chemotherapeutics.

MMPs play important roles in the development and maintenance of neuropathic pain, including mechanical allodynia [111]. Recent studies have demonstrated that MMPs are activated in DRGs leading to neuroinflammation and neuropathic pain [111, 112]. Tonello et al. showed that intrathecal injections of a monoclonal antibody targeting MMP-9 significantly prevent and reverse paclitaxel-induced mechanical allodynia in male and female mice, by decreasing oxidative stress and neuroinflammatory mediators IL-6 and tTNF α, as well as preventing paclitaxel-induced loss of IENF [113]. These findings suggest MMPs as a new target in paclitaxel-induced PN. Andecaliximab is a humanized anti-MMP-9 monoclonal antibody for the treatment of gastric cancer and ulcerative colitis [114] and may serve as a dual therapeutic approach, on the one hand, to treat tumor progression and on the other hand to reduce CIPN symptoms.

EQ-6 (6-(5-amino)-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline hydrochloride), a novel analog of the known antioxidant ethoxyquin, prevents axonal degeneration in primary DRG neurons and epidermal nerve fiber loss *in vitro* and in a murine model of paclitaxel-induced CIPN, respectively. Cetinkaya-Fisgin et al. demonstrated that this axonal protection is associated with preserved levels of nicotinamide adenine dinucleotide, a key metabolite in the programmed pathway of axonal degeneration [115].

Additional studies are still needed to confirm the benefits of these novel agents in the prevention of CIPN before they can be introduced into clinical practice. Many aspects of complementary approaches still need to be considered in terms of their safety, drug interactions, and cost-effectiveness.

Treatment strategies

Consistent with the above information about preventive strategies, there is currently no clearly effective treatment for CIPN. Therefore, after the onset of CIPN, the first step remains modification of the schedule, which could be aligned with the potential increased risk of cancer recurrence and mortality. Symptomatic therapy approaches focus on managing symptoms by reducing pain, improving physical functioning, and positively influencing the quality of life. Overview of the pharmacological and non-pharmacological treatment options are listed below and therapy recommendations for CIPN by leading guidelines of expert societies are summarized in Table 4.

Antidepressants. The antidepressant duloxetine, which acts as serotonin and norepinephrine reuptake inhibitor, can effectively alleviate the symptoms of CIPN without reducing the antitumor activity of antineoplastic agents [116, 117]. In patients with peripheral neuropathy following anticancer drugs, duloxetine was administered due to its proven efficacy in neuropathic pain of other origins [118–121]. Duloxetine was found to have a better effect in reducing the severity of neuropathic pain and the degree of motor neuropathy compared to other therapeutic approaches and was also reported to have fewer side effects compared to other drugs in this indication, such as venlafaxine. In addition, patients treated with oxaliplatin are more likely to benefit from duloxetine than patients with paclitaxel-induced PN, suggesting that the effect of duloxetine may be closely related to the specific molecular mechanisms underlying oxaliplatin-induced PN [122]. A large, randomized trial demonstrated a moderate clinical benefit in patients with painful CIPN treated with duloxetine vs. placebo, with a higher rate of pain reduction (59% vs. 38%) [123]. Matsuoka et al. investigated the efficacy of duloxetine for CINP patients unresponsive or intolerant to the opioid-pregabalin combination. In a multicenter, randomized, double-blind, placebo-controlled trial, they found that the addition of duloxetine to opioid-pregabalin therapy may have a clinical benefit in reducing refractory CINP, but further studies are needed to verify the efficacy of the addition of duloxetine [124]. However, another research group [125] on the contrary reported that pregabalin has higher CIPN-attenuating efficacy than duloxetine, improved sensory neuropathy more significantly than duloxetine, and was also more beneficial in improving neurotoxicity questionnaire scores. Since the efficacy of duloxetine was not confirmed in approximately 40% of patients [122] and up to 14.7% of patients in a Japanese study discontinued duloxetine due to adverse effects such as fatigue and nausea [126], there is a greater need to offer additional strategies for the treatment of CIPN. Saito et al. reported a case report of a patient with eribulin-induced PN who received duloxetine in combination with the selective α2δ ligand, mirogabalin [127]. As the mechanisms of mirogabalin and duloxetine attenuating CIPN are different, the authors suggested that the additive and synergistic effects of this combination influenced the results of their study. The combined therapy of duloxetine with other substances with analgetic effect may represent a promising strategy, especially in patients intolerant to high doses of duloxetine or patients unresponsive to previous treatment.

In a randomized clinical trial, another serotonin-norepinephrine reuptake inhibitor venlafaxine demonstrated clinical activity against oxaliplatin-induced acute neurosensory toxicity. Thus, venlafaxine can be used in individual cases in the treatment of CIPN, as there are studies that indicate a significant benefit compared to placebo, although with several side effects, including asthenia and nausea [128, 129].

Amitriptyline, a tricyclic antidepressant that enhances noradrenergic and serotonergic neurotransmission by blocking the noradrenaline and serotonin transporters at presynaptic terminals, represents the gold standard in the treatment of various pain syndromes from neuropathic pain through fibromyalgia to migraine and tension headaches [130]. A double-blinded, randomized, placebo-controlled study evaluated the effectiveness of low-dose amitriptyline in relieving chemotherapy-induced symptoms. The

Table 4. Selected agents evaluated for treatment of CIPN.

Agent	Frequent side effects	Recommendation	Limitations	Ref.
Pharmacological approaches				
Duloxetine	nausea, dry mouth, somnolence, headache, anxiety	recommended	not specified	[122, 123]
Venlafaxine	nausea, dry mouth, somnolence, headache, anxiety, hypertension	recommended	not specified	[128, 129]
Amitriptyline	drowsiness, fatigue, dizziness, hypotension, weight gain	not recommended	small trials, negative study results	[131]
Gabapentin	somnolence, dizziness, vertigo	not recommended	negative trial	[135]
Pregabalin	drowsiness, somnolence, peripheral edema, weight gain	recommended	many side effects	[136]
Lamotrigine	headache, drowsiness, dizziness	not recommended	negative trial	[209]
Carbamazepine	hyponatremia, drug interactions	not recommended	small trials, many side effects	[137, 210]
Oxycodone	sedation, dizziness, headache, constipation, nausea, itch, dependency, abuse	recommended-as a 3rd option	high risk of tolerance	[138]
Naproxen	confusion, headache, tiredness, drowsiness, dizziness	recommended with gabapentin and pregabalin	recommended only in combination	[211]
Indomethacin-pregabalin	fewer side effects than monotherapy	potential therapeutic advantages	recommended only in combination	[212]
Meloxicam-pregabalin	fewer side effects than monotherapy	potential therapeutic advantages	recommended only in combination	[212]
Nabiximols	psychosis-inducing potential	not recommended	negative trial, many side effects	[147]
Topical therapies				
CBD oil/cream	not specified	recommended	small sample size	[163, 164]
10% amitriptyline cream	skin irritation	recommended	small sample size, lack of a control group	[132]
Lidocaine patch	burning, erythema, pruritus, or skin irritations at the application site	recommended-as a 2nd option	in case of localized neuropathic pain, or oral drug intolerance	[213, 214]
Capsaicin patch	pain or erythema, burning sensation at the application site	recommended	in case of localized neuropathic pain	[168]
Baclofen, amitriptyline, and ketamine gel	not specified	not recommended	not statistically significant trial compared toa placebo	[172]
1% menthol cream	not specified	recommended	in case of localized neuropathic pain	[174]
Non-Pharmacological approaches				
Acupuncture	not specified	recommended	not specified	[176, 177]
Exercise	no side effects	recommended	not specified	[175]
Scrambler therapy	contact dermatitis	recommended	small trials	[178]

study revealed negative results or only a mild improvement in CIPN symptoms and showed that amitriptyline did not improve sensory neuropathic symptoms. No statistical significance was achieved, probably due to the small number of patients and the too low dose of amitriptyline. Amitriptyline in low doses was well tolerated, nevertheless, potential side effects, drug interactions, and cardiac toxicity in higher doses should be considered in the risk-benefit analysis [131]. Additionally, Rossignol et al. investigated the effect of 10% amitriptyline cream on neuropathic pain. Given the limited efficacy of systemic venlafaxine in CIPN and its safety profile, topical amitriptyline 10% appears to be a good candidate for first-line treatment of CIPN, allowing the continuation of chemotherapy at effective doses [132].

Anticonvulsants. Gabapentin is a commonly used antiepileptic drug, structurally related to the neurotransmitter gamma-aminobutyric acid (GABA). In recent years, its effectiveness in the treatment of several neuropathic syndromes has been demonstrated. Nerve excitability that occurs after nerve injury is thought to be mediated by upregulation of the α2δ1 subunit of voltage-gated calcium channels in DRG neurons [133]. When gabapentin inhibits the α2δ1 subunit, it reduces calcium influx and neurotransmitter release from nerve endings, and thus theoretically provides a basis for reducing nociception in neuropathic syndromes [134]. Rao et al. investigated the efficacy of gabapentin administration in cancer patients in a double-blind, placebo-controlled study in patients with CIPN. They did not reveal any improvement

in pain intensity or sensory neuropathy in patients taking gabapentin [135].

Amino acid derivate of GABA, pregabalin, binds to α2δ subunits of voltage-gated calcium channels, reduces calcium influx and neurotransmitter release. Mishra et al. showed in their study that pregabalin has better effectiveness than gabapentin as well as a placebo in the therapy of cancer patients with CIPN [136]. Although gabapentin and pregabalin have been shown to be effective in the treatment of polyneuropathies in many studies as well as in clinical practice, there is limited scientific evidence on the efficacy of these agents in the treatment of anti-cancer drugs-induced peripheral neuropathy. Moreover, side effects after their use include frequent dizziness, drowsiness, and somnolence [136].

The anticonvulsant drug carbamazepine is currently the best-studied treatment and drug of choice in the treatment of trigeminal neuralgia. Carbamazepine acts by inhibiting voltage-gated sodium channels, thereby reducing nerve membrane excitability and potentiating GABA receptors, which may be relevant for its efficacy in neuropathic pain. However, due to little evidence and frequent side effects such as sedation, dizziness, nausea, vomiting, diplopia, memory problems, ataxia, elevated liver enzymes, and hyponatremia, carbamazepine cannot be recommended for the treatment of neuropathic pain [137].

Analgesics. According to several recommendations, low- and high-efficacy opioids may be considered as a third option in the treatment of neuropathic pain of any origin, although side effects, development of tolerance, and misuse may be limiting. Overall, the response of neuropathic pain to opioid treatment is low, but oxycodone administration during chemotherapy has been associated with a reduced incidence of CIPN [138]. Non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), metamizole, or paracetamol have low efficacy in the treatment of neuropathic pain and their long-term use is associated with various potential side effects such as nephrotoxicity or hepatotoxicity. However, peripheral nerve damage and neuropathic pain may result from increased tissue pressure due to swelling of the legs and arms and have been described as a consequence of chronic venous insufficiency. Only in these cases, NSAID treatment may be effective and recommended in reducing swelling and corresponding pain [139].

Other drugs. Olodanrigan (EMA401) is a highly selective, orally active angiotensin II type 2 receptor antagonist. It was developed for the therapy of neuropathic pain and in a few past years was tested in clinical trials for effectiveness in CIPN patients [140–142]. Olodanrigan (EMA401) analgesic action appears to involve inhibition of DRG neuron hyperexcitability. However, the clinical studies performed so far in patients with CIPN have not yielded reproducible conclusions and are therefore unconvincing and difficult to interpret [143].

Oxaliplatin treatment alters the activities of voltage-gated ion channels and ligand-gated ion channels, such as transient receptor potential (TRP) channels and their cold-responsive subtypes, TRP melastatin 8 and TRP ankyrin 1, which also contribute to oxaliplatin-induced hypersensitivity to cold [144]. Acetazolamide and topiramate are known inhibitors of carbonic anhydrase, which facilitates intracellular pH homeostasis. These agents inhibit the lowering of cytosolic pH and TRP ankyrin 1 sensitization by oxaliplatin without affecting the tumor-killing effect, potentially preventing oxaliplatin-induced cold allodynia [141].

Cannabinoids suppress central [145] and peripheral [146] sensitization, which is thought to be involved in pathological pain. This suggests a possible mechanism underlying the effectiveness of cannabinoids in suppressing CIPN. Nabiximols, an oral mucosal cannabinoid spray, has been evaluated to relieve CIPN symptoms. In this clinical study, the authors found no indication of differences in neuropathy scores between the active drugs and placebo, but patients taking nabiximols suffered from various side effects such as dizziness, nausea, fatigue, and dry mouth, which significantly reduced interest in this approach. In general, cannabinoids are not recommended for the treatment of neuropathic pain of any origin because efficacy is low and the rate of side effects such as addiction is high. Cannabinoid therapy may be considered for multimodal pain therapy in individual cases and when other therapeutic options fail [147].

The well-known anti-inflammatory and anti-nociceptive effects of PEA (palmitoylethanolamide) are considered a beneficial strategy in the management of the oxaliplatin- [148] and paclitaxel- [149] induced CIPN model, as well as in osteoarthritis [150] and fibromyalgia studies [151]. Cristiano et al. demonstrated that um-PEA (ultramicronized PEA) reduced the development of hypersensitivity with an effect associated with the reduction of the spinal cord and hippocampal pro-inflammatory cytokines, as well as antidepressant and anxiolytic effects [152].

Recently, the importance of the ceramide-S1P rheostat regulating neuronal function and neuroimmune interactions in the development of neuropathic pain has been studied. In this context, hope has been raised for a new treatment of neuropathic pain disorders with fingolimod, an S1P receptor modulator currently being investigated in several trials for the management of CIPN [153, 154].

Sigma-1 receptor (S1R) is a transmembrane protein found in the endoplasmic reticulum, specifically at the mitochondria-associated endoplasmic reticulum membrane, which plays a key role in neuroprotection against CIPN [155]. MR309, a novel selective S1R antagonist, was tested in a phase II, randomized, placebo-controlled trial in ameliorating oxaliplatin-induced PN [156]. MR309 treatment was associated with significantly reduced severe chronic neuropathy with an acceptable safety profile and showed a potential neuroprotective role for chronic oxaliplatin-induced PN.

Exchange proteins regulated by cAMP (Epacs) are cAMP-binding proteins known to play a pivotal role in mechanical allodynia induced by nerve injury and inflammation [157]. Pooja et al. demonstrated reduced paclitaxel-induced mechanical allodynia, astrocyte activation, and intraepidermal nerve fiber loss, in Epac1-knockout mice as compared to wild-type mice. Moreover, the Epac-inhibitor ESI-09 reversed paclitaxel-induced mechanical allodynia, suppressed spinal cord astrocyte activation in the spinal cord, and protected against IENF loss, as well as blocked paclitaxel-induced abnormal spontaneous discharges in DRG neurons in wild-type mice, which indicates Epac1 in nociceptors as a novel potential target for the treatment of CIPN [158].

Paclitaxel induces Schwann cells' dedifferentiation, thereby impairing the ability of Schwann cells to form myelin [159]. On the contrary, intracellular cyclic adenosine monophosphate (cAMP) plays an essential role in Schwann cells' differentiation [160, 161], and therefore phosphodiesterase (PDE) inhibitors that increase intracellular cAMP could attenuate paclitaxel-induced dedifferentiation of Schwann cells. Cilostazol, a selective PDE3 inhibitor, potently inhibited paclitaxel-induced dedifferentiation of cultured Schwann cells through cAMP/Epac signaling and attenuated mechanical hypersensitivity and Schwann cells' dedifferentiation in the sciatic nerve in a murine model of paclitaxel-related CIPN [162]. Koyanagi et al. concluded that cilostazol suppresses paclitaxel-related CIPN without limiting the anticancer effect of paclitaxel, thus representing a new strategy for the treatment of other demyelinating peripheral neuropathies as well [162].

Topical therapies. As many systemic treatment options are still unconvincing, have great interaction potential when co-administered with chemotherapeutic agents and their dose needs to be slowly titrated from a low starting dose to the therapeutic dose providing the best efficacy and limited side effects, topical treatment is of particular importance in this context. Topical treatment options for neuropathic pain include cannabinoids, lidocaine, and capsaicin patches, and various gel formulations.

Although the systemic use of cannabinoids in the treatment of CIPN is not recommended due to several limitations, recently the benefits of topical cannabidiol (CBD) in the form of oil, creams, or ointments have been increasingly discussed. Xu et al. conducted a double-blind, randomized, placebo-controlled study to investigate the efficacy of topically applied CBD oil in the symptomatic treatment of chronic pain in peripheral neuropathy of the lower extremities. The authors demonstrated a statistically significant reduction in intense and sharp pain, as well as cold and itchy sensations [163]. D'Andre et al. presented a case series of patients with CIPN who used topical creams containing the cannabinoids delta-nine-tetrahydrocannabinol (THC) and/or CBD. They suggested that cannabinoids may be helpful for patients with chemotherapy-induced peripheral neuropathy. Patients described a partial decrease in painful CIPN symptoms with the onset of perceived benefit in about 10 to 15 minutes. Given that there is great heterogeneity in the compounds observed in cannabis, as well as in the concentration and type of cannabis in available topical creams, a randomized placebo-controlled trial of a standardized product is needed to determine the true utility of this approach for the treatment of CIPN [164].

Lidocaine, an anesthetic drug that has been used for local nerve block and epidural anesthesia in a wide variety of superficial and invasive procedures since 1948, was recognized in the 1980s as a drug to relieve peripheral neuropathic pain [165]. The main mechanism of action is the blockade of voltage-gated sodium channels, which are considered to be the main target of lidocaine. Lidocaine can reduce peak sodium channel currents and accelerate the inactivation process to reduce neuronal excitability and thus preventing and reducing pain. The lidocaine patch is approved for the treatment of postherpetic neuralgia but can also be used to treat localized neuropathic pain of other origins such as CIPN [166]. However, randomized clinical trial demonstrating efficacy in CIPN is still lacking, and therefore lidocaine patches are used as a second option in the treatment of peripheral neuropathic pain, especially in the case of oral drug intolerance.

Capsaicin is a naturally occurring substance derived from plants of the genus *Capsicum*, approved as second-line therapy for the topical treatment of neuropathic pain. Capsaicin is known to act on the cation channel with TRP, a member of the vanilloid subfamily 1, which is involved in somatic and visceral peripheral inflammation, modulation of nociceptive inputs to spinal cord and brainstem centers, and integration of various painful stimuli [167]. Capsaicin 8% patch is the only topical skin application that provides effective pain relief with good tolerability, a favorable safety profile, and a low risk of systemic side effects. The effect is comparable to established oral drugs and capsaicin can be used as monotherapy or in combination with other pharmaceutical products for the treatment of pain. Anand et al. demonstrated a significant reduction in spontaneous, touch-induced, cold-induced, and overall pain in cancer patients treated with a 30-minute application of a capsaicin 8%-foot patch [168].

Barton et al. performed a clinical study to evaluate the effect of three topical analgesics on CIPN symptoms. Baclofen, amitriptyline, and ketamine have complementary mechanisms of action that elicit three different pathways that may provide additive or synergistic relief from neuropathic symptoms. Baclofen is a GABA receptor agonist [169], amitriptyline affects adenosine A receptors and sodium channels [170], and ketamine inhibits NMDA receptors [171]. Topical gel treatment with baclofen (0.8%), amitriptyline (3%), and ketamine (1.5%) was beneficial in a randomized, double-blind clinical trial compared to a placebo, but the overall effect was mild and not clinically relevant. A clinical

study with this topical cream twice daily for 6 days in cancer patients with CIPN was well tolerated, with no evidence of systemic toxicity, but revealed no significant effect on pain, numbness, or tingling [172].

Significant reduction of pain and functional improvement in patients with CIPN was detected upon topical therapy with 1% menthol cream twice daily. A new potential therapeutic approach demonstrated that endogenous neural circuitry underlying cooling-induced analgesia may represent a novel target for intervention. Specific molecular receptors for cooling have been identified in sensory nerves with evidence for their upregulation in neuropathic pain models [173]. Authors identified that activation of one of these, the TRP melastatin 8 ion channel, by topical agents, such as menthol, produced significant analgesia. Fallon et al. indicate the therapeutic potential of topical menthol for CIPN-related pain. Authors however recommend further systematic evaluation of efficacy, because of a small cohort of patients and non-blinded study [174].

Non-pharmacological approaches. Current data suggest that exercise is an affordable, safe, and promising supportive measure for cancer patients with CIPN. A study examining a 10-week home muscle strengthening and balancing program compared to regular care found a significant reduction in neuropathic pain in patients in the exercise group compared to those in the regular care group [175].

Studies evaluating the efficacy of acupuncture and electroacupuncture in the treatment of CIPN over the control group found significant improvements in clinical neurological evaluation, improved pain interference, neurotoxicity-related symptoms, as well as improved physical and functional well-being during the 20-week evaluation [176, 177].

Scrambler therapy (ST) is an electrocutaneous pain relief treatment that appears to be effective in reducing chronic neuropathic pain without any significant side effects. Treatment is performed with standard electrocardiographic skin electrodes placed above and below the pain site, and the ST device directs electrical signals across the field to simulate pain-free information. In a randomized clinical trial, the effect of a 30-minute ST session for two weeks was evaluated compared to patients with standard care. ST-treated patients showed improved pain, tingling, and numbness compared to controls [178].

In conclusion, various types of anticancer drugs are commonly used to treat cancer, either alone or in combination with other drugs. Peripheral neuropathy is the most common, dose-limiting side effect of anticancer treatment that adversely affects patients' quality of life and chemotherapy progress. The ideal treatment strategy for CIPN should act as a multi-targeting agent to increase its protective efficacy against neuropathy without reducing the antitumor efficacy of chemotherapy. Although there are several promising potential therapies for the prevention and treatment of CIPN, and several potential drugs are still in clinical trials, the need to improve the effectiveness of individual clinical approaches remains very substantial. In this review, we discussed the preventive and therapeutic properties of various agents and their pharmacological potential as drugs in the treatment of chemotherapy-induced peripheral neuropathy. We focused on both pharmacological and non-pharmacological approaches, demonstrating the high safety of therapy without serious side effects and promising potential in previously published studies. Furthermore, the prevention and treatment of CIPN remain unmet, and further quality research is essential to achieve effective and reliable results and to improve the rational discovery of new therapeutic and preventive approaches with the potential to prevent or weaken the development of CIPN.

Acknowledgments: This work was supported by the Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic (No. VEGA 2/0123/20, VEGA 2/0109/21).

References

[1] PARK SB, GOLDSTEIN D, KRISHNAN AV, LIN CS, FRIEDLANDER ML et al. Chemotherapy-induced peripheral neurotoxicity: A critical analysis: CIPN: A Critical Analysis. CA Cancer J Clin 2013; 63: 419–437. https://doi.org/10.3322/caac.21204

[2] WILKES G. Peripheral Neuropathy Related to Chemotherapy. Semin Oncol Nurs 2007; 23: 162–173. https://doi.org/10.1016/j.soncn.2007.05.001

[3] BONOMO R, CAVALETTI G. Clinical and biochemical markers in CIPN: A reappraisal. Rev Neurol (Paris) 2021; 177: 890–907. 2021. https://doi.org/10.1016/j.neurol.2020.11.001

[4] SAŁAT K. Chemotherapy-induced peripheral neuropathy: part 1-current state of knowledge and perspectives for pharmacotherapy. Pharmacol Rep 2020; 72: 486–507. https://doi.org/10.1007/s43440-020-00109-y

[5] HERSHMAN DL, LACCHETTI C, DWORKIN RH, LAVOIE SMITH EM, BLEEKER J et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. JCO 2014; 32: 1941–1967. https://doi.org/10.1200/JCO.2013.54.0914

[6] BAKITAS MA. Background Noise: The Experience of Chemotherapy-Induced Peripheral Neuropathy. Nurs Res 2007; 56: 323–331. https://doi.org/10.1097/01.NNR.0000289503.22414.79

[7] SPECK RM, DEMICHELE A, FARRAR JT, HENNESSY S, MAO JJ et al. Scope of symptoms and self-management strategies for chemotherapy-induced peripheral neuropathy in breast cancer patients. Support Care Cancer 2012; 20: 2433–2439. https://doi.org/10.1007/s00520-011-1365-8

[8] TOFTHAGEN C. Patient Perceptions Associated With Chemotherapy-Induced Peripheral Neuropathy. Clin J Oncol Nurs 2010; 14: E22–E28. https://doi.org/10.1188/10.CJON.E22-E28

[9] SERETNY M, CURRIE GL, SENA ES, RAMNARINE S, GRANT R, MACLEOD MR et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain 2014; 155: 2461–2470. https://doi.org/10.1016/j.pain.2014.09.020

[10] BRIANI C, ARGYRIOU AA, IZQUIERDO C, VELASCO R, CAMPAGNOLO M et al. Long-term course of oxaliplatin-induced polyneuropathy: a prospective 2-year follow-up study: Briani et al. J Peripher Nerv Syst 2014; 19: 299–306. https://doi.org/10.1111/jns.12097

[11] RIVERA DR, GANZ PA, WEYRICH MS, BANDOS H, MELNIKOW J. Chemotherapy-Associated Peripheral Neuropathy in Patients With Early-Stage Breast Cancer: A Systematic Review. JNCI: Journal of the National Cancer Institute 2018; 110: djx140. https://doi.org/10.1093/jnci/djx140

[12] MAIHÖFNER C, DIEL I, TESCH H, QUANDEL T, BARON R. Chemotherapy-induced peripheral neuropathy (CIPN): current therapies and topical treatment option with high-concentration capsaicin. Support Care Cancer 2021; 29: 4223–4238. https://doi.org/10.1007/s00520-021-06042-x

[13] MARMIROLI P, RIVA B, POZZI E, BALLARINI E, LIM D et al. Susceptibility of different mouse strains to oxaliplatin peripheral neurotoxicity: Phenotypic and genotypic insights. PLoS ONE 2017; 12: e0186250. https://doi.org/10.1371/journal.pone.0186250

[14] CLIFF J, JORGENSEN AL, LORD R, AZAM F, COSSAR L et al. The molecular genetics of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2017; 120: 127–140. https://doi.org/10.1016/j.critrevonc.2017.09.009

[15] LEBLANC AF, SPROWL JA, ALBERTI P, CHIORAZZI A, ARNOLD WD et al. OATP1B2 deficiency protects against paclitaxel-induced neurotoxicity. J Clin Invest 2018; 128: 816–825. https://doi.org/10.1172/JCI96160

[16] LEE KH, CHANG HJ, HAN SW, OH DY, IM SA et al. Pharmacogenetic analysis of adjuvant FOLFOX for Korean patients with colon cancer. Cancer Chemother Pharmacol 2013; 71: 843–851. https://doi.org/10.1007/s00280-013-2075-3

[17] JOHNSON C, PANKRATZ VS, VELAZQUEZ AI, AAKRE JA, LOPRINZI CL et al. Candidate pathway-based genetic association study of platinum and platinum-taxane related toxicity in a cohort of primary lung cancer patients. J Neurol Sci 2015; 349: 124–128. https://doi.org/10.1016/j.jns.2014.12.041

[18] BOYETTE-DAVIS JA, HOU S, ABDI S, DOUGHERTY PM. An updated understanding of the mechanisms involved in chemotherapy-induced neuropathy. Pain Manag 2018; 8: 363–375. https://doi.org/10.2217/pmt-2018-0020

[19] MA J, KAVELAARS A, DOUGHERTY PM, HEIJNEN CJ. Beyond symptomatic relief for chemotherapy-induced peripheral neuropathy: Targeting the source: Novel Therapeutic Strategies for CIPN. Cancer 2018; 124: 2289–2298. https://doi.org/10.1002/cncr.31248

[20] STAROBOVA H, VETTER I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. Front Mol Neurosci 2017; 10: 174. https://doi.org/10.3389/fnmol.2017.00174

[21] GIESSEN-JUNG C, VON BAUMGARTEN L. Chemotherapie-induzierte periphere Neuropathie. Dtsch Med Wochenschr 2018;113: 970–978. https://doi.org/10.1055/s-0043-120839

[22] RICHARDSON PG, BRIEMBERG H, JAGANNATH S, WEN PY, BARLOGIE B et al. Frequency, Characteristics, and Reversibility of Peripheral Neuropathy During Treatment of Advanced Multiple Myeloma With Bortezomib. J Clin Oncol 2006; 24: 3113–3120. https://doi.org/10.1200/JCO.2005.04.7779

[23] KOMIYA Y, TASHIRO T. Effects of taxol on slow and fast axonal transport. Cell Motil. Cytoskeleton 1988; 11: 151–156. https://doi.org/10.1002/cm.970110302

[24] KIRCHMAIR R, WALTER DH, II M, RITTIG K, TIETZ AB et al. Antiangiogenesis Mediates Cisplatin-Induced Peripheral Neuropathy: Attenuation or Reversal by Local Vascular Endothelial Growth Factor Gene Therapy Without Augmenting Tumor Growth. Circulation 2005; 111: 2662–2670. https://doi.org/10.1161/CIRCULATIONAHA.104.470849

[25] LISSE TS, ELIAS LJ, PELLEGRINI AD, MARTIN PB, SPAULDING EL et al. Paclitaxel-induced epithelial damage and ectopic MMP-13 expression promotes neurotoxicity in zebrafish. Proc Natl Acad Sci U S A 2016; 113: E2189–2198. https://doi.org/10.1073/pnas.1525096113

[26] ALLEN DT, KIERNAN JA. Permeation of proteins from the blood into peripheral nerves and ganglia. Neuroscience 1994; 59: 755–764. https://doi.org/10.1016/0306-4522(94)90192-9

[27] TREPEL M. Neuroanatomie: Struktur und Funktion, 5. Aufl. München. Elsevier, Urban & Fischer 2012, p. 173. ISBN 978-3437412998

[28] CHAUDHRY V, CORNBLATH DR, POLYDEFKIS M, FERGUSON A, BORRELLO I. Characteristics of bortezomib- and thalidomide-induced peripheral neuropathy. J Peripher Nerv Syst 2008; 13: 275–282. https://doi.org/10.1111/j.1529-8027.2008.00193.x

[29] QUASTHOFF S, HARTUNG HP. Chemotherapy-induced peripheral neuropathy. J Neurol 2002; 249: 9–17. https://doi.org/10.1007/PL00007853

[30] SITTL R, LAMPERT A, HUTH T, SCHUY ET, LINK AS et al. Anticancer drug oxaliplatin induces acute cooling-aggravated neuropathy via sodium channel subtype Na V 1.6-resurgent and persistent current. Proc Natl Acad Sci USA 2012; 109: 6704–6709. https://doi.org/10.1073/pnas.1118058109

[31] SIAU C, BENNETT GJ. Dysregulation of Cellular Calcium Homeostasis in Chemotherapy-Evoked Painful Peripheral Neuropathy. Anesth Analg 2006; 102: 1485–1490. https://doi.org/10.1213/01.ane.0000204318.35194.ed

[32] POUPON L, LAMOINE S, PEREIRA V, BARRIERE DA, LOLIGNIER S et al. Targeting the TREK-1 potassium channel via riluzole to eliminate the neuropathic and depressive-like effects of oxaliplatin. Neuropharmacology 2018; 140: 43–61. https://doi.org/10.1016/j.neuropharm.2018.07.026

[33] AVAN A, POSTMA TJ, CERESA C, AVAN A, CAVALETTI G et al. Platinum-Induced Neurotoxicity and Preventive Strategies: Past, Present, and Future. Oncologist 2015; 20: 411–432. https://doi.org/10.1634/theoncologist.2014-0044

[34] PORUCHYNSKY MS, SACKETT DL, ROBEY RW, WARD Y, ANNUNZIATA C et al. Proteasome inhibitors increase tubulin polymerization and stabilization in tissue culture cells: A possible mechanism contributing to peripheral neuropathy and cellular toxicity following proteasome inhibition. Cell Cycle 2008;7: 940–949. https://doi.org/10.4161/cc.7.7.5625

[35] MACFARLANE BV, WRIGHT A, BENSON HAE. Reversible Blockade of Retrograde Axonal Transport in the Rat Sciatic Nerve by Vincristine. J Pharm Pharmacol 2011; 49: 97–101. https://doi.org/10.1111/j.2042-7158.1997.tb06759.x

[36] THEISS C, MELLER K. Taxol impairs anterograde axonal transport of microinjected horseradish peroxidase in dorsal root ganglia neurons in vitro. Cell Tissue Res 2000; 299: 213–224. https://doi.org/10.1007/s004419900120

[37] GAMPER N, OOI L. Redox and Nitric Oxide-Mediated Regulation of Sensory Neuron Ion Channel Function. Antioxid Redox Signal 2015; 22: 486–504. https://doi.org/10.1089/ars.2014.5884

[38] DOYLE T, CHEN Z, MUSCOLI C, BRYANT L, ESPOSITO E et al. Targeting the Overproduction of Peroxynitrite for the Prevention and Reversal of Paclitaxel-Induced Neuropathic Pain. J Neurosci 2012; 32: 6149–6160. https://doi.org/10.1523/JNEUROSCI.6343-11.2012

[39] TOYAMA S, SHIMOYAMA N, ISHIDA Y, KOYASU T, SZETO HH et al. Characterization of Acute and Chronic Neuropathies Induced by Oxaliplatin in Mice and Differential Effects of a Novel Mitochondria-targeted Antioxidant on the Neuropathies. Anesthesiology 2014; 120: 459–473. https://doi.org/10.1097/01.anes.0000435634.34709.65

[40] HAN Y, SMITH MT. Pathobiology of cancer chemotherapy-induced peripheral neuropathy (CIPN). Front Pharmacol 2013; 4: 156. https://doi.org/10.3389/fphar.2013.00156

[41] KIRCHMAIR R, TIETZ AB, PANAGIOTOU E, WALTER DH, SILVER M et al. Therapeutic Angiogenesis Inhibits or Rescues Chemotherapy-induced Peripheral Neuropathy: Taxol- and Thalidomide-induced Injury of Vasa Nervorum is Ameliorated by VEGF. Mol Ther 2007; 15: 69–75. https://doi.org/10.1038/sj.mt.6300019

[42] KOLÁCNÁ L, BAKESOVÁ J, VARGA F, KOSTÁKOVÁ E, PLÁNKA L et al. Biochemical and biophysical aspects of collagen nanostructure in the extracellular matrix. Physiol Res 2007; 56: S51–S60. https://doi.org/10.33549/physiolres.931302

[43] LI Y, ZHANG H, ZHANG H, KOSTURAKIS AK, JAWAD AB, DOUGHERTY PM. Toll-Like Receptor 4 Signaling Contributes to Paclitaxel-Induced Peripheral Neuropathy. J Pain 2014; 15: 712–725. https://doi.org/10.1016/j.jpain.2014.04.001

[44] ZHANG H, BOYETTE-DAVIS JA, KOSTURAKIS AK, LI Y, YOON SY et al. Induction of Monocyte Chemoattractant Protein-1 (MCP-1) and Its Receptor CCR2 in Primary Sensory Neurons Contributes to Paclitaxel-Induced Peripheral Neuropathy. J Pain 2013; 14: 1031–1044. https://doi.org/10.1016/j.jpain.2013.03.012

[45] BABCOCK AA, KUZIEL WA, RIVEST S, OWENS T. Chemokine Expression by Glial Cells Directs Leukocytes to Sites of Axonal Injury in the CNS. J. Neurosci 2003; 23: 7922–7930. https://doi.org/10.1523/JNEUROSCI.23-21-07922.2003

[46] WOOLF CJ, ALLCHORNE A, SAFIEH-GARABEDIAN B, POOLE S. Cytokines, nerve growthfactor and inflammatory hyperalgesia: the contribution of tumour necrosis factor α: TNF α , IL-1 β , NGF and inflammatory hyperalgesia. Br J Pharmacol 1997;121: 417–424. https://doi.org/10.1038/sj.bjp.0701148

[47] BINSHTOK AM, WANG H, ZIMMERMANN K, AMAYA F, VARDEH D et al. Nociceptors Are Interleukin-1 Sensors. J Neurosci 2008; 28: 14062–14073. https://doi.org/10.1523/JNEUROSCI.3795-08.2008

[48] SORKIN LS, XIAO WH, WAGNER R, MYERS RR. Tumour necrosis factor-α induces ectopic activity in nociceptive primary afferent fibres. Neurosci 1997; 81: 255–262. https://doi.org/10.1016/S0306-4522(97)00147-4

[49] ÖZAKTAY C, CAVANAUGH J, ASIK I, DELEO J, WEINSTEIN J. Dorsal root sensitivity to interleukin-1 beta, interleukin-6 and tumor necrosisfactor in rats. Eur Spine J 2002; 11: 467–475. https://doi.org/10.1007/s00586-002-0430-x

[50] MCMAHON SB, CAFFERTY WBJ, MARCHAND F. Immune and glialcell factors as painmediators and modulators. Exp Neurol 2005; 192: 444–462. https://doi.org/10.1016/j.expneurol.2004.11.001

[51] ZHANG H, NEI H, DOUGHERTY PM. A p38 Mitogen-Activated Protein Kinase-Dependent Mechanism of Disinhibition in Spinal Synaptic Transmission Induced by Tumor Necrosis Factor. J Neurosci 2010; 30: 12844–12855. https://doi.org/10.1523/JNEUROSCI.2437-10.2010

[52] TEUFEL A, ZHAN T, HÄRTEL N, BORNSCHEIN J, EBERT MP et al. Management of immune related adverse events induced by immune checkpoint inhibition. Cancer Lett 2019; 456: 80–87. https://doi.org/10.1016/j.canlet.2019.04.018

[53] YOKOSUKA T, TAKAMATSU M, KOBAYASHI-IMANISHI W, HASHIMOTO-TANE A, AZUMA M et al. Programmed cell death 1 forms negative costimulatory microclusters that directly inhibit T cell receptor signaling by recruiting phosphatase SHP2. J of Exp Med 2012; 209: 1201–1217. https://doi.org/10.1084/jem.20112741

[54] SPAIN L, DIEM S, LARKIN J. Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev 2016; 44: 51–60. https://doi.org/10.1016/j.ctrv.2016.02.001

[55] DULOS J, CARVEN GJ, VAN BOXTEL SJ, EVERS S, DRIESSEN-ENGELS LJ et al. PD-1 Blockade Augments Th1 and Th17 and Suppresses Th2 Responses in Peripheral Blood From Patients With Prostate and Advanced Melanoma Cancer. J Immunother 2012; 35: 169–178. https://doi.org/10.1097/CJI.0b013e318247a4e7

[56] JOHNSON DB, BALKO JM. Biomarkers for Immunotherapy Toxicity: Are Cytokines the Answer? Clin Cancer Res 2019; 25: 1452–1454. https://doi.org/10.1158/1078-0432.CCR-18-3858

[57] THOMPSON JA, SCHNEIDER BJ, BRAHMER J, ANDREWS S, ARMAND P et al. Management of Immunotherapy-Related Toxicities, Version 1.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019; 17: 255–289. https://doi.org/10.6004/jnccn.2019.0013

[58] ADDINGTON J, FREIMER M. Chemotherapy-induced peripheral neuropathy: an update on the current understanding. F1000Res 2016; 5: 1466. https://doi.org/10.12688/f1000research.8053.1

[59] MCCRARY JM, GOLDSTEIN D, BOYLE F, COX K, GRIMISON P et al. Optimal clinical assessment strategies for chemotherapy-induced peripheral neuropathy (CIPN): a systematic review and Delphi survey. Support Care Cancer 2017; 25: 3485–3493. https://doi.org/10.1007/s00520-017-3772-y

[60] HAUSHEER FH, SCHILSKY RL, BAIN S, BERGHORN EJ, LIEBERMAN F. Diagnosis, Management, and Evaluation of Chemotherapy-Induced Peripheral Neuropathy. Seminars in Oncology 2006; 33: 15–49. https://doi.org/10.1053/j.seminoncol.2005.12.010

[61] HAANPÄÄ M, ATTAL N, BACKONJA M, BARON R, BENNETT M et al. NeuPSIG guidelines on neuropathic pain assessment. Pain 2011; 152: 14–27. https://doi.org/10.1016/j.pain.2010.07.031

[62] BARON R, BINDER A, WASNER G. Neuropathicpain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010; 9: 807–819. https://doi.org/10.1016/S1474-4422(10)70143-5

[63] FREYNHAGEN R, BARON R, GOCKEL U, TÖLLE TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006; 22: 1911–1920. https://doi.org/10.1185/030079906X132488

[64] BOUHASSIRA D, ATTAL N, ALCHAAR H, BOUREAU F, BROCHET B et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005; 114: 29–36. https://doi.org/10.1016/j.pain.2004.12.010

[65] CAVALETTI G, FRIGENI B, LANZANI F, MATTAVELLI L, SUSANI E et al. Chemotherapy-Induced Peripheral Neurotoxicity assessment: A critical revision of the currently available tools. Eur J Cancer 2010; 46: 479–494. https://doi.org/10.1016/j.ejca.2009.12.008

[66] LUCKETT T, KING MT, BUTOW PN, OGUCHI M, RANKIN N et al. Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. Ann Oncol 2011; 22: 2179–2190. https://doi.org/10.1093/annonc/mdq721

[67] SMITH EML, KNOERL R, YANG JJ, KANZAWA-LEE G, LEE D et al. In Search of a Gold Standard Patient-Reported Outcome Measure for Use in Chemotherapy- Induced Peripheral Neuropathy Clinical Trials. Cancer Control 2018; 25: 107327481875660. https://doi.org/10.1177/1073274818756608

[68] SMITH EML, BANERJEE T, YANG JJ, BRIDGES CM, ALBERTI P et al. Psychometric Testing of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale Using Pooled Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization and Alliance for Clinical Trials in Oncology A151408 Study Data. Cancer Nurs 2019; 42: 179–189. https://doi.org/10.1097/NCC.0000000000000596

[69] MENDOZA TR, WANG XS, WILLIAMS LA, SHI Q, VICHAYA EG et al. Measuring Therapy-Induced Peripheral Neuropathy: Preliminary Development and Validation of the Treatment-Induced Neuropathy Assessment Scale. J Pain 2015; 16: 1032–1043. https://doi.org/10.1016/j.jpain.2015.07.002

[70] KNOERL R, GRAY E, STRICKER C, MITCHELL SA, KIPPE K et al. Electronic versus paper-pencil methods for assessing chemotherapy-induced peripheral neuropathy. Support Care Cancer 2017; 25: 3437–3446. https://doi.org/10.1007/s00520-017-3764-y

[71] LAURIA G, DEVIGILI G. Skin biopsy as a diagnostic tool in peripheralneuropathy. Nat Rev Neurol 2007;3: 546–557. https://doi.org/10.1038/ncpneuro0630

[72] TANKISI H, PUGDAHL K, JOHNSEN B, FUGLSANG-FREDERIKSEN A. Correlations of nerve conduction measures in axonal and demyelinating polyneuropathies. Clin Neurophysiol 2007;118: 2383–2392. https://doi.org/10.1016/j.clinph.2007.07.027

[73] PERKINS BA, LOVBLOM LE, BRIL V, SCARR D, OSTROVSKI I et al. Corneal confocal microscopy for identification of diabetic sensorimotor polyneuropathy: a pooled multinational consortium study. Diabetologia 2018; 61: 1856–1861. https://doi.org/10.1007/s00125-018-4653-8

[74] LEWIS EJH, LOVBLOM LE, FERDOUSI M, HALPERN EM, JEZIORSKA M et al. Rapid Corneal Nerve Fiber Loss: A Marker of Diabetic Neuropathy Onset and Progression. Diabetes Care 2020; 43: 1829–1835. https://doi.org/10.2337/dc19-0951

[75] ARGYRIOU AA, PARK SB, ISLAM B, TAMBURIN S, VELASCO R et al. Neurophysiological, nerve imaging and other techniques to assess chemotherapy-induced peripheral neurotoxicity in the clinical and research settings. J Neurol Neurosurg Psychiatry 2019; 90: 1361–1369. https://doi.org/10.1136/jnnp-2019-320969

[76] CHIANG JCB, GOLDSTEIN D, TRINH T, AU K, MIZRAHI D et al. A Cross-Sectional Study of Sub-Basal Corneal Nerve Reduction Following Neurotoxic Chemotherapy. Trans Vis Sci Technol 2021; 10: 24. https://doi.org/10.1167/tvst.10.1.24

[77] MEREGALLI C, FUMAGALLI G, ALBERTI P, CANTA A, CHIORAZZI A et al. Neurofilament light chain: a specific serum biomarker of axonal damage severity in rat models of Chemotherapy-Induced Peripheral Neurotoxicity. Arch Toxicol 2020; 94: 2517–2522. https://doi.org/10.1007/s00204-020-02755-w

[78] CAMPONE M, BERTON-RIGAUD D, JOLY-LOBBEDEZ F, BAURAIN JF, ROLLAND F et al. A Double-Blind, Randomized Phase II Study to Evaluate the Safety and Efficacy of Acetyl-L-Carnitine in the Prevention of Sagopilone-Induced Peripheral Neuropathy. Oncologist 2013; 18: 1190–1191. https://doi.org/10.1634/theoncologist.2013-0061

[79] GUO Y, JONES D, PALMER JL, FORMAN A, DAKHIL SR et al. Oral alpha-lipoic acid to prevent chemotherapy-induced peripheral neuropathy: a randomized, double-blind, placebo-controlled trial. Support Care Cancer 2014; 22: 1223–1231. https://doi.org/10.1007/s00520-013-2075-1

[80] SHINDE SS, SEISLER D, SOORI G, ATHERTON PJ, PACHMAN DR et al. Can pregabalin prevent paclitaxel-associated neuropathy? -An ACCRU pilot trial. Support Care Cancer 2016; 24: 547–553. https://doi.org/10.1007/s00520-015-2807-5

[81] SALEHI Z, ROAYAEI M.Effect of Vitamin E on oxaliplatin-induced peripheral neuropathy prevention: A randomized controlled trial. Int J Prev Med 2015; 6: 104. https://doi.org/10.4103/2008-7802.169021

[82] SCHLOSS JM, COLOSIMO M, AIREY C, MASCI P, LINNANE AWet al. A randomised, placebo-controlled trial assessing the efficacy of an oral B group vitamin in preventing the development of chemotherapy-induced peripheral neuropathy (CIPN). Support Care Cancer 2017; 25: 195–204. https://doi.org/10.1007/s00520-016-3404-y

[83] JORDAN B, JAHN F, BECKMANN J, UNVERZAGT S, MÜLLER-TIDOW C et al. Calcium and Magnesium Infusions for the Prevention of Oxaliplatin-Induced Peripheral Neurotoxicity: A Systematic Review. Oncology 2016; 90: 299–306. https://doi.org/10.1159/000445977

[84] GREENLEE H, CREW KD, CAPODICE J, AWAD D, BUONO D et al. Randomized sham-controlled pilot trial of weekly electro-acupuncture for the prevention of taxane-induced peripheral neuropathy in women with early stage breast cancer. Breast Cancer Res Treat 2016; 156: 453–464. https://doi.org/10.1007/s10549-016-3759-2

[85] CANTA A, CHIORAZZI A, POZZI E, FUMAGALLI G, MONZA L et al. Calmangafodipir Reduces Sensory Alterations and Prevents Intraepidermal Nerve Fibers Loss in a Mouse Model of Oxaliplatin Induced Peripheral Neurotoxicity. Antioxidants 2020; 9: 594. https://doi.org/10.3390/antiox9070594

[86] EL-FATATRY BM, IBRAHIM OM, HUSSIEN FZ, MOSTAFA TM. Role of metformin in oxaliplatin-induced peripheral neuropathy in patients with stage III colorectal cancer: randomized, controlled study. Int J Colorectal Dis 2018; 33: 1675–1683. https://doi.org/10.1007/s00384-018-3104-9

[87] NGUYEN VH, LAWRENCE HJ. Use of Gabapentin in the Prevention of Taxane-Induced Arthralgias and Myalgias. J Clin Oncol 2004; 22: 1767–1769. https://doi.org/10.1200/JCO.2004.99.298

[88] ALTAF R, LUND BRIXEN A, KRISTENSEN B, NIELSEN SE. Incidence of Cold-InducedPeripheral Neuropathy and Dose Modification of Adjuvant Oxaliplatin-Based Chemotherapy for Patients with Colorectal Cancer. Oncology 2014; 87: 167–172. https://doi.org/10.1159/000362668

[89] BEIJERS AJM, MOLS F, TJAN-HEIJNEN VCG, FABER CG, VAN DE POLL-FRANSE LV et al. Peripheral neuropathy in colorectal cancer survivors: The influence of oxaliplatin administration. Results from thepopulation-based PROFILES registry. Acta Oncol 2015; 54: 463–469. https://doi.org/10.3109/0284186X.2014.980912

[90] BEIJERS AJM, BONHOF CS, MOLS F, OPHORST J, DE VOS-GEELEN J et al. Multicenter randomized controlled trial to evaluate the efficacy and tolerability of frozen gloves for the prevention of chemotherapy-induced peripheral neuropathy. Ann Oncol 2020; 31: 131–136. https://doi.org/10.1016/j.annonc.2019.09.006

[91] TSUYUKI S, YAMAGAMI K, YOSHIBAYASHI H, SUGIE T, MIZUNO Y et al. Effectiveness and safety of surgical glove compression therapy as a prophylactic method against nanoparticle albumin-bound-paclitaxel-induced peripheral neuropathy. Breast 2019; 47: 22–27. https://doi.org/10.1016/j.breast.2019.06.008

[92] SUNDAR R, BANDLA A, TAN S, KUMARAKULASINGHE NB, HUANG Y et al. Cryocompression for enhanced limb hypothermia in preventing paclitaxel-induced peripheral neuropathy. J Clin Oncol 2018; 36: 10095–10095. https://doi.org/10.1200/JCO.2018.36.15_suppl.10095

[93] DUREGON F, VENDRAMIN B, BULLO V, GOBBO S, CUGUSI L et al. Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. Crit Rev Oncol Hematol 2018; 121: 90–100. https://doi.org/10.1016/j.critrevonc.2017.11.002

[94] ZIMMER P, TREBING S, TIMMERS-TREBING U, SCHENK A, PAUST R et al. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. Support Care Cancer 2018. 26: 615–624. https://doi.org/10.1007/s00520-017-3875-5

[95] BALDUCCI S, IACOBELLIS G, PARISI L, DI BIASE N, CALANDRIELLO E et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. J Diabetes Complications 2006; 20: 216–223. https://doi.org/10.1016/j.jdiacomp.2005.07.005

[96] DERKSEN TME, BOURS MJL, MOLS F, WEIJENBERG MP. Lifestyle-Related Factors in the Self-Management of Chemotherapy-Induced Peripheral Neuropathy in Colorectal Cancer: A Systematic Review. Evid Based Complement Alternat Med 2017; 2017: 1–14. https://doi.org/10.1155/2017/7916031

[97] RIVAT C, RICHEBÉ P, LABOUREYRAS E, LAULIN JP, HAVOUIS R et al. Polyamine deficient diet to relieve pain hypersensitivity. Pain 2008; 137: 125–137. https://doi.org/10.1016/j.pain.2007.08.021

[98] JI RR, KOHNO T, MOORE KA, WOOLF CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci 2003; 26: 696–705. https://doi.org/10.1016/j.tins.2003.09.017

[99] BALAYSSAC D, FERRIER J, PEREIRA B, GILLET B, PÉTORIN C et al. Prevention of oxaliplatin-induced peripheral neuropathy by a polyamine-reduced diet--NEUROXAPOL: protocol of a prospective, randomised, controlled, single-blind and monocentric trial. BMJ Open 2015; 5: e007479–e007479. https://doi.org/10.1136/bmjopen-2014-007479

[100] GEWANDTER JS, GIBBONS CH, CAMPAGNOLO M, LEE J, CHAUDARI J et al. Clinician-rated measures for distal symmetrical axonal polyneuropathy: ACTTION systematic review. Neurology 2019; 93: 346–360. https://doi.org/10.1212/WNL.0000000000007974

[101] ARSLAN S, ZORBA BAHCELI P, İLIK Y, ARTAÇ M. The preliminary effects of henna on chemotherapy-induced peripheral neuropathy in women receiving oxaliplatin-based treatment: A parallel-group, randomized, controlled pilot trial. Eur J Oncol Nurs 2020; 48: 101827. https://doi.org/10.1016/j.ejon.2020.101827

[102] GILLEY J, RIBCHESTER RR, COLEMAN MP. Sarm1 Deletion, but Not WldS, Confers Lifelong Rescue in a Mouse Model of Severe Axonopathy. Cell Rep 2017; 21: 10–16. https://doi.org/10.1016/j.celrep.2017.09.027

[103] GERDTS J, SUMMERS DW, SASAKI Y, DIANTONIO A, MILBRANDT J. Sarm1-mediated axon degeneration requires both SAM and TIR interactions. J Neurosci 2013; 33: 13569–13580. https://doi.org/10.1523/JNEUROSCI.1197-13.2013

[104] OSTERLOH JM, YANG J, ROONEY TM, FOX AN, ADALBERT R et al. dSarm/Sarm1 is required for activation of an injury-induced axon death pathway. Science 2012; 337: 481–484. https://doi.org/10.1126/science.1223899

[105] KRAUSS R, BOSANAC T, DEVRAJ R, ENGBER T, HUGHES RO. Axons Matter: The Promise of Treating Neurodegenerative Disorders by Targeting SARM1-Mediated Axonal Degeneration. Trends Pharmacol Sci 2020; 41: 281–293. https://doi.org/10.1016/j.tips.2020.01.006

[106] BOSANAC T, HUGHES RO, ENGBER T, DEVRAJ R, BREARLEY A et al. Pharmacological SARM1 inhibition protects axon structure and function in paclitaxel-induced peripheral neuropathy. Brain 2021; 144: 3226–3238. https://doi.org/10.1093/brain/awab184

[107] SAŁAT K. Chemotherapy-induced peripheral neuropathy-part 2: focus on the prevention of oxaliplatin-induced neurotoxicity. Pharmacol Rep 2020; 72: 508–527. https://doi.org/10.1007/s43440-020-00106-1

[108] SCHWARZ S, LEHMBECKER A, TONGTAKO W, HAHN K, WANG Y et al. Neurotrophic effects of GM1 ganglioside, NGF, and FGF2 on canine dorsal root ganglia neurons in vitro. Sci Rep 2020; 10: 5380. https://doi.org/10.1038/s41598-020-61852-z

[109] SU Y, HUANG J, WANG S, UNGER JM, ARIAS-FUENZALIDA J et al. The Effects of Ganglioside-Monosialic Acid in Taxane-Induced Peripheral Neurotoxicity in Patients with Breast Cancer: A Randomized Trial. J Natl Cancer Inst 2020; 112: 55–62. https://doi.org/10.1093/jnci/djz086

[110] WU S, BAI X, GUO C, HUANG Z, OUYANG H et al. Ganglioside-monosialic acid (GM1) for prevention of chemotherapy-induced peripheral neuropathy: a meta-analysis with trial sequential analysis. BMC Cancer 2021; 21: 1173. https://doi.org/10.1186/s12885-021-08884-4

[111] KAWASAKI Y, XU ZZ, WANG X, PARK JY, ZHUANG ZY et al. Distinct roles of matrix metalloproteases in the early- and late-phase development of neuropathic pain. Nat Med 2008; 14: 331–336. https://doi.org/10.1038/nm1723

[112] JIANG L, PAN CL, WANG CY, LIU BQ, HAN Y et al. Selective suppression of the JNK-MMP2/9 signal pathway by tetramethylpyrazine attenuates neuropathic pain in rats. J Neuroinflammation 2017; 14: 174. https://doi.org/10.1186/s12974-017-0947-x

[113] TONELLO R, LEE SH, BERTA T. Monoclonal Antibody Targeting the Matrix Metalloproteinase 9 Prevents and Reverses Paclitaxel-Induced Peripheral Neuropathy in Mice. J Pain 2019; 20: 515–527. https://doi.org/10.1016/j.jpain.2018.11.003

[114] AMAR S, FIELDS GB. Potential clinical implications of recent matrix metalloproteinase inhibitor design strategies. Expert Rev Proteomics 2015; 12: 445–447. https://doi.org/10.1586/14789450.2015.1069190

[115] CETINKAYA-FISGIN A, ZHU J, LUAN X, KIM JS, OH B et al. Development of EQ-6, a Novel Analogue of Ethoxyquin to Prevent Chemotherapy-Induced Peripheral Neuropathy. Neurotherapeutics 2021; 18: 2061–2072. https://doi.org/10.1007/s13311-021-01093-8

[116] LOPRINZI CL, LACCHETTI C, BLEEKER J, CAVALETTI G, CHAUHAN C et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. J Cancer Oncol 2020; 38: 3325–3348. https://doi.org/10.1200/JCO.20.01399

[117] JORDAN B, MARGULIES A, CARDOSO F, CAVALETTI G, HAUGNES HS et al. Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO–EONS–EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. Ann Oncol 2020; 31: 1306–1319. https://doi.org/10.1016/j.annonc.2020.07.003

[118] BRIL V, ENGLAND J, FRANKLIN GM, BACKONJA M, COHEN J et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011; 76: 1758–1765. https://doi.org/10.1212/WNL.0b013e3182166ebe

[119] GOLDSTEIN DJ, LU Y, DETKE MJ, LEE TC, IYENGAR S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain 2005; 116: 109–118. https://doi.org/10.1016/j.pain.2005.03.029

[120] WERNICKE JF, PRITCHETT YL, D'SOUZA DN, WANINGER A, TRAN P et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006; 67: 1411–1420. https://doi.org/10.1212/01.wnl.0000240225.04000.1a

[121] RASKIN J, PRITCHETT YL, WANG F, D'SOUZA DN, WANINGER AL et al. A Double-Blind, Randomized Multicenter Trial Comparing Duloxetine with Placebo in the Management of Diabetic Peripheral Neuropathic Pain. Pain Med 2005; 6: 346–356. https://doi.org/10.1111/j.1526-4637.2005.00061.x

[122] SMITH EM, PANG H, CIRRINCIONE C, FLEISHMAN S, PASKETT ED et al. Effect of Duloxetine on Pain, Function, and Quality of Life Among Patients With Chemotherapy-Induced Painful Peripheral Neuropathy: A Randomized Clinical Trial. JAMA 2013; 309: 1359. https://doi.org/10.1001/jama.2013.2813

[123] SMITH EM, PANG H, YE C, CIRRINCIONE C, FLEISHMAN S et al. Predictors of duloxetine response in patients with oxaliplatin-induced painful chemotherapy-induced peripheral neuropathy (CIPN): a secondary analysis of randomised controlled trial – CALGB/alliance 170601. Eur J Cancer Care 2017; 26: e12421. https://doi.org/10.1111/ecc.12421

[124] MATSUOKA H, IWASE S, MIYAJI T, KAWAGUCHI T, ARIYOSHI K et al. Additive Duloxetine for Cancer-Related Neuropathic Pain Nonresponsive or Intolerant to Opioid-Pregabalin Therapy: A Randomized Controlled Trial (JORTC-PAL08). J Pain Symptom Manage 2019; 58: 645–653. https://doi.org/10.1016/j.jpainsymman.2019.06.020

[125] SALEHIFAR E, JANBABAEI G, HENDOUEI N, ALIPOUR A, TABRIZI N et al. Comparison of the Efficacy and Safety of Pregabalin and Duloxetine in Taxane-Induced Sensory Neuropathy: A Randomized Controlled Trial. Clin Drug Investig 2020; 40: 249–257. https://doi.org/10.1007/s40261-019-00882-6

[126] HIRAYAMA Y, ISHITANI K, SATO Y, IYAMA S, TAKADA K et al. Effect of duloxetine in Japanese patients with chemotherapy-induced peripheral neuropathy: a pilot randomized trial. Int J Clin Oncol 2015; 20: 866–871. https://doi.org/10.1007/s10147-015-0810-y

[127] SAITO Y, TAKEKUMA Y, OSHINO T, SUGAWARA M. Combination of Mirogabalin and Duloxetine Attenuates Peripheral Neuropathy by Eribulin: A Novel Case Report. Case Rep Oncol 2022; 15: 606–610. https://doi.org/10.1159/000525059

[128] DURAND JP, DEPLANQUE G, MONTHEIL V, GORNET JM, SCOTTE F et al. Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol 2012; 23: 200–205. https://doi.org/10.1093/annonc/mdr045

[129] ZIMMERMAN C, ATHERTON PJ, PACHMAN D, SEISLER D, WAGNER-JOHNSTON N et al. MC11C4: a pilot randomized, placebo-controlled, double-blind study of venlafaxine to prevent oxaliplatin-induced neuropathy. Support Care Cancer 2016; 24: 1071–1078. https://doi.org/10.1007/s00520-015-2876-5

[130] JACKSON KC, ST ONGE EL. Antidepressant Pharmacotherapy: Considerations for the Pain Clinician. Pain Practice 2003; 3: 135–143. https://doi.org/10.1046/j.1533-2500.2003.03020.x

[131] KAUTIO AL, HAANPÄÄ M, SAARTO T, KALSO E. Amitriptyline in the Treatment of Chemotherapy-Induced Neuropathic Symptoms. Journal of Pain and Symptom Management 2008; 35: 31–39. https://doi.org/10.1016/j.jpainsymman.2007.02.043

[132] ROSSIGNOL J, COZZI B, LIEBAERT F, HATTON S, VIALLARD ML et al. High concentration of topical amitriptyline for treating chemotherapy-induced neuropathies. Support Care Cancer 2019; 27: 3053–3059. https://doi.org/10.1007/s00520-018-4618-y

[133] LUO ZD, CHAPLAN SR, HIGUERA ES, SORKIN LS, STAUDERMAN KA et al. Upregulation of Dorsal Root Ganglion α 2 δ Calcium Channel Subunit and Its Correlation with Allodynia in Spinal Nerve-Injured Rats. J. Neurosci 2001; 21: 1868–1875. https://doi.org/10.1523/JNEUROSCI.21-06-01868.2001

[134] SHIMOYAMA M, SHIMOYAMA N, HORI Y. Gabapentin affects glutamatergic excitatory neurotransmission in the rat dorsal horn. Pain 2000; 85: 405–414. https://doi.org/10.1016/S0304-3959(99)00283-3

[135] RAO RD, MICHALAK JC, SLOAN JA, LOPRINZI CL, SOORI GS et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: A phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer 2007; 110: 2110–2118. https://doi.org/10.1002/cncr.23008

[136] MISHRA S, BHATNAGAR S, GOYAL GN, RANA SPS, UPADHYA SP. A Comparative Efficacy of Amitriptyline, Gabapentin, and Pregabalin in Neuropathic Cancer Pain: A Prospective Randomized Double-Blind Placebo-Controlled Study. Am J Hosp Palliat Care 2012; 29: 177–182. https://doi.org/10.1177/1049909111412539

[137] AL-QULITI KW. Update on neuropathic pain treatment for trigeminal neuralgia: The pharmacological and surgical options. Neurosciences (Riyadh) 2015; 20: 107–114. https://doi.org/10.17712/nsj.2015.2.20140501

[138] NAGASHIMA M, OOSHIRO M, MORIYAMA A, SUGISHITA Y, KADOYA K et al. Efficacy and tolerability of controlled-release oxycodone for oxaliplatin-induced peripheral neuropathy and the extension of FOLFOX therapy in advanced colorectal cancer patients. Support Care Cancer 2014; 22: 1579–1584. https://doi.org/10.1007/s00520-014-2132-4

[139] REINHARDT F, WETZEL T, VETTEN S, RADESPIEL-TRÖGER M, HILZ MJ et al. Peripheral neuropathy in chronic venous insufficiency. Muscle Nerve 2000; 23: 883–887. https://doi.org/10.1002/(SICI)1097-4598(200006)23:6<883::AID-MUS6>3.0.CO;2-T

[140] YAMAMOTO S, USHIO S, EGASHIRA N, KAWASHIRI T, MITSUYASU S et al. Excessive spinal glutamate transmission is involved in oxaliplatin-induced mechanical allodynia: a possibility for riluzole as a prophylactic drug. Sci Rep 2017; 7: 9661. https://doi.org/10.1038/s41598-017-08891-1

[141] POTENZIERI A, B. RIVA B, GENAZZANI A. Unexpected Ca2+-mobilization of oxaliplatin via H1 histamine receptors. Cell Calcium 2020; 86: 102128. https://doi.org/10.1016/j.ceca.2019.102128

[142] XU D, ZHAO H, GAO H, ZHAO H, LIU D, et al. Participation of pro-inflammatory cytokines in neuropathic pain evoked by chemotherapeutic oxaliplatin via central GABAergic pathway. Mol Pain 2018; 14: 174480691878353. https://doi.org/10.1177/1744806918783535

[143] YANG Y, ZHAO B, GAO X, SUN J, YE J et al. Targeting strategies for oxaliplatin-induced peripheral neuropathy: clinical syndrome, molecular basis, and drug development. J Exp Clin Cancer Res 2021; 40: 331. https://doi.org/10.1186/s13046-021-02141-z

[144] MARMIROLI P, CAVALETTI G, CAROZZI V, RIVA B, LIM D et al. Calcium-related Neurotoxicity of Oxaliplatin: Understanding the Mechanisms to Drive Therapy. Curr Med Chem 2015; 22: 3682–3694. https://doi.org/10.2174/0929867322666151001121302

[145] NACKLEY AG, ZVONOK AM, MAKRIYANNIS A, HOHMANN AG. Activation of Cannabinoid CB 2 Receptors Suppresses C-Fiber Responses and Windup in Spinal Wide Dynamic Range Neurons in the Absence and Presence of Inflammation. J Neurophysiol 2004; 92: 3562–3574. https://doi.org/10.1152/jn.00886.2003

[146] KHASABOVA IA, KHASABOV S, PAZ J, HARDING-ROSE C, SIMONE DA et al. Cannabinoid Type-1 Receptor Reduces Pain and Neurotoxicity Produced by Chemotherapy. J Neurosci 2012;32: 7091–7101. https://doi.org/10.1523/JNEUROSCI.0403-12.2012

[147] LYNCH ME, CESAR-RITTENBERG P, HOHMANN AG. A Double-Blind, Placebo-Controlled, Crossover Pilot Trial With Extension Using an Oral Mucosal Cannabinoid Extract for Treatment of Chemotherapy-Induced Neuropathic Pain. J Pain Symptom Manage 2014; 47: 166–173. https://doi.org/10.1016/j.jpainsymman.2013.02.018

[148] DI CESARE MANNELLI L, PACINI A, CORTI F, BOCCELLA S, LUONGO L et al. Antineuropathic Profile of N-Palmitoylethanolamine in a Rat Model of Oxaliplatin-Induced Neurotoxicity. PLoS ONE 2015; 10: e0128080. https://doi.org/10.1371/journal.pone.0128080

[149] DONVITO G, WILKERSON JL, DAMAJ MI, LICHTMAN AH. Palmitoylethanolamide Reverses Paclitaxel-Induced Allodynia in Mice. J Pharmacol Exp Ther 2016; 359: 310–318. https://doi.org/10.1124/jpet.116.236182

[150] STEELS E, VENKATESH R, STEELS E, VITETTA G, VITETTA L. A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis. Inflammopharmacology 2019; 27: 475–485. https://doi.org/10.1007/s10787-019-00582-9

[151] DEL GIORNO R, KAPER S, PALADINI A, VARRASSI G, COACCIOLI S. Palmitoylethanolamide in Fibromyalgia: Results from Prospective and Retrospective Observational Studies. Pain Ther 2015; 4: 169–178. https://doi.org/10.1007/s40122-015-0038-6

[152] CRISTIANO C, AVAGLIANO C, CUOZZO M, LIGUORI FM, CALIGNANO A et al. The Beneficial Effects of Ultramicronized Palmitoylethanolamide in the Management of Neuropathic Pain and Associated Mood Disorders Induced by Paclitaxel in Mice. Biomolecules 2022; 12: 1155. https://doi.org/10.3390/biom12081155

[153] JANES K, LITTLE JW, LI C, BRYANT L, CHEN C et al. The Development and Maintenance of Paclitaxel-induced Neuropathic Pain Require Activation of the Sphingosine 1-Phosphate Receptor Subtype 1. J Biol Chem 2014; 289: 21082–21097. https://doi.org/10.1074/jbc.M114.569574

[154] LANGESLAG M, KRESS M. The ceramide-S1P pathway as a druggable target to alleviate peripheral neuropathic pain. Expert Opin Ther Targets 2020; 24: 869–884. https://doi.org/10.1080/14728222.2020.1787989

[155] SU TP, SU TC, NAKAMURA Y, TSAI SY. The Sigma-1 Receptor as a Pluripotent Modulator in Living Systems. Trends Pharmacol Sci 2016; 37: 262–278. https://doi.org/10.1016/j.tips.2016.01.003

[156] BRUNA J, VIDELA S, ARGYRIOU AA, VELASCO R, VILLORIA J et al. Efficacy of a Novel Sigma-1 Receptor Antagonist for Oxaliplatin-Induced Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Phase IIa Clinical Trial. Neurotherapeutics 2018; 15: 178–189. https://doi.org/10.1007/s13311-017-0572-5

[157] ALMAHARIQ M, CHAO C, MEI FC, HELLMICH MR, PATRIKEEV I et al. Pharmacological inhibition and genetic knockdown of exchange protein directly activated by cAMP 1 reduce pancreatic cancer metastasis in vivo. Mol Pharmacol 2015; 87: 142–149. https://doi.org/10.1124/mol.114.095158

[158] SINGHMAR P, HUO X, LI Y, DOUGHERTY PM, MEI F et al. Orally active Epac inhibitor reverses mechanical allodynia and loss of intraepidermal nerve fibers in a mouse model of chemotherapy-induced peripheral neuropathy. Pain 2018;159: 884–893. https://doi.org/10.1097/j.pain.0000000000001160

[159] IMAI S, KOYANAGI M, AZIMI Z, NAKAZATO Y, MATSUMOTO M et al. Taxanes and platinum derivatives impair Schwann cells via distinct mechanisms. Sci Rep 2017; 7: 5947. https://doi.org/10.1038/s41598-017-05784-1

[160] HAN SH, YUN SH, SHIN YK, PARK HT, PARK JI. Heat Shock Protein 90 is Required for cAMP-Induced Differentiation in Rat Primary Schwann Cells. Neurochem Res 2019; 44: 2643–2657. https://doi.org/10.1007/s11064-019-02885-3

[161] SOHN EJ, PARK HT, SHIN YK. Exosomes derived from differentiated Schwann cells inhibit Schwann cell migration via microRNAs. Neuroreport 2020; 31: 515–522. https://doi.org/10.1097/WNR.0000000000001435

[162] KOYANAGI M, IMAI S, IWAMITSU Y, MATSUMOTO M, SAIGO M et al. Cilostazol is an effective causal therapy for preventing paclitaxel-induced peripheral neuropathy by suppression of Schwann cell dedifferentiation. Neuropharmacology 2021; 188: 108514. https://doi.org/10.1016/j.neuropharm.2021.108514

[163] XU DH, CULLEN BD, TANG M, FANG Y. The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities. Curr Pharm Biotechnol 2020; 21: 390–402, 2020, https://doi.org/10.2174/1389201020666191202111534

[164] D'ANDRE S, MCALLISTER S, NAGI J, GIRIDHAR KV, RUIZ-MACIAS E et al. Topical Cannabinoids for Treating Chemotherapy-Induced Neuropathy: A Case Series. Integr Cancer Ther 2021; 20: 15347354211061740. https://doi.org/10.1177/15347354211061739

[165] GOZALO-MARCILLA M, GASTHUYS F, SCHAUVLIEGE S. Partial intravenous anaesthesia in the horse: a review of intravenous agents used to supplement equine inhalation anaesthesia. Part 1: lidocaine and ketamine. Vet Anaesth Analg 2014; 41: 335–345. https://doi.org/10.1111/vaa.12179

[166] STUBBLEFIELD MD, BURSTEIN HJ, BURTON AW, CUSTODIO CM, DENG GEet al.NCCN Task Force Report: Management of Neuropathy in Cancer. J Natl Compr Canc Netw 2009; 7: S-1–S-26. https://doi.org/10.6004/jnccn.2009.0078

[167] FRIAS B, MERIGHI A. Capsaicin, Nociception and Pain. Molecules 2016; 21: 797. https://doi.org/10.3390/molecules21060797

[168] ANAND P, ELSAFA E, PRIVITERA R, NAIDOO K, YIANGOU Yet al. Rational treatment of chemotherapy-induced peripheral neuropathy with capsaicin 8% patch: from pain relief towards disease modification. J Pain Res 2019; 12: 2039–2052. https://doi.org/10.2147/JPR.S213912

[169] FRANEK M, VACULÍN S, ROKYTA R. GABA(B) receptor agonist baclofen has non-specific antinociceptive effect in the model of peripheral neuropathy in the rat. Physiol Res 2004; 53: 351–355, 2004.
[170] LYNCH ME, CLARK AJ, SAWYNOK J. A Pilot Study Examining Topical Amitriptyline, Ketamine, and a Combination of Both in the Treatment of Neuropathic Pain. The Clinical J Pain 2003; 19: 323–328. https://doi.org/10.1097/00002508-200309000-00007
[171] GAMMAITONI A, GALLAGHER RM, WELZ-BOSNA M. Topical Ketamine Gel: Possible Role in Treating Neuropathic Pain: Table 1. Pain Med 2000; 1: 97–100. https://doi.org/10.1046/j.1526-4637.2000.00006.x
[172] BARTON DL, WOS EJ, QIN R, MATTAR BI, GREEN NB et al. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. Support Care Cancer 2011; 19: 833–841. https://doi.org/10.1007/s00520-010-0911-0
[173] EID SR, CORTRIGHT DN. Transient Receptor Potential Channels on Sensory Nerves. Sensory Nerves 2009; 194: 261–281. https://doi.org/10.1007/978-3-540-79090-7_8
[174] FALLON MT, STOREY DJ, KRISHAN A, WEIR CJ, MITCHELL R. Cancer treatment-related neuropathic pain: proof of concept study with menthol—a TRPM8 agonist. Support Care Cancer 2015; 23: 2769–2777. https://doi.org/10.1007/s00520-015-2642-8
[175] DHAWAN S, ANDREWS R, KUMAR L, WADHWA S, SHUKLA G. A Randomized Controlled Trial to Assess the Effectiveness of Muscle Strengthening and Balancing Exercises on Chemotherapy-Induced Peripheral Neuropathic Pain and Quality of Life Among Cancer Patients. Cancer Nurs 2020; 43: 269–280. https://doi.org/10.1097/NCC.0000000000000693
[176] ROSTOCK M, JAROSLAWSKI K, GUETHLIN C, LUDTKE R, SCHRÖDER S et al. Chemotherapy-induced peripheral neuropathy in cancer patients: a four-arm randomized trial on the effectiveness of electroacupuncture. Evid Based Complement Alternat Med 2013; 2013: 349653. https://doi.org/10.1155/2013/349653
[177] LU W, GIOBBIE-HURDER A, FREEDMAN RA, SHIN IH, LIN NU et al. Acupuncture for Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer Survivors: A Randomized Controlled Pilot Trial. Oncologist 2020; 25: 310–318. https://doi.org/10.1634/theoncologist.2019-0489
[178] SMITH TJ, RAZZAK AR, BLACKFORD AL, ENSMINGER J, SAIKI CA et al. Pilot Randomized Sham-Controlled Trial of MC5-A Scrambler Therapy in the Treatment of Chronic Chemotherapy-Induced Peripheral Neuropathy (CIPN). J Palliat Care 2020; 35: 53–58. https://doi.org/10.1177/0825859719827589
[179] ANDRÉ T, BONI C, MOUNEDJI-BOUDIAF L, NAVARRO M, TABERNERO J et al. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. N Engl J Med 2004; 350: 2343–2351. https://doi.org/10.1056/NEJMoa032709
[180] WILSON RH, LEHKY T, THOMAS RR, QUINN MG, FLOETER MK et al. Acute Oxaliplatin-Induced Peripheral Nerve Hyperexcitability. J Cancer Oncol 2002; 20: 1767–1774. https://doi.org/10.1200/JCO.2002.07.056
[181] KANAT O, ERTAS H, CANER B. Platinum-induced neurotoxicity: A review of possible mechanisms. World J Clin Oncol 2017; 8: 329. https://doi.org/10.5306/wjco.v8.i4.329
[182] AMPTOULACH S, TSAVARIS N. Neurotoxicity Caused by the Treatment with Platinum Analogues. Chemother Res Pract 2011; 2011: 1–5. https://doi.org/10.1155/2011/843019
[183] STEVENS SM, MCCLELLAND CM, TRUSHEIM JE, LEE MS. Carboplatin-associated Cranial Neuropathy. Neuroophthalmology 2018; 42: 302–305. https://doi.org/10.1080/01658107.2017.1419367
[184] HANAI A, ISHIGURO H, SOZU T, TSUDA M, YANO I et al. Effects of Cryotherapy on Objective and Subjective Symptoms of Paclitaxel-Induced Neuropathy: Prospective Self-Controlled Trial. J Natl Cancer Inst 2018; 110: 141–148. https://doi.org/10.1093/jnci/djx178
[185] BENNEDSGAARD K, VENTZEL L, ANDERSEN NT, THEMISTOCLEOUS AC, BENNETT DL et al. Oxaliplatin- and docetaxel-induced polyneuropathy: clinical and neurophysiological characteristics," J Peripher Nerv Syst 2020; 25: 377–387. https://doi.org/10.1111/jns.12413
[186] ECKHOFF L, KNOOP AS, JENSEN MB, EJLERTSEN B, EWERTZ M. Risk of docetaxel-induced peripheral neuropathy among 1,725 Danish patients with early stage breast cancer. Breast Cancer Res Treat 2013; 142: 109–118. https://doi.org/10.1007/s10549-013-2728-2
[187] NORONHA V, PRABHASH K, JOSHI A. Beyond ten cycles of cabazitaxel for castrate-resistant prostate cancer. Indian J Cancer 2014; 51: 363. https://doi.org/10.4103/0019-509X.146721
[188] CASEY EB, JELLIFE AM, LE QUESNE PM, MILLETT YL. Vincristine neuropathy: clinical and electrophysiological observations. Brain 1973; 96: 69–86. https://doi.org/10.1093/brain/96.1.69
[189] CORTES J, MONTERO AJ, GLÜCK S. Eribulin mesylate, a novel microtubule inhibitor in the treatment of breast cancer. Cancer Treat Rev 2012; 38: 143–151. https://doi.org/10.1016/j.ctrv.2011.03.006
[190] TSURUTANI J, SAKATA Y, MATSUOKA T. Chemotherapy-induced peripheral neuropathy in breast cancer patients treated with eribulin: interim data from a post-marketing observational study. Breast Cancer 2019; 26: 235–243. https://doi.org/10.1007/s12282-018-0919-8
[191] BENBOW SJ, WOZNIAK KM, KULESH B, SAVAGE A, SLUSHER BS, LITTLEFIELD BA et al. Microtubule-Targeting Agents Eribulin and Paclitaxel Differentially Affect Neuronal Cell Bodies in Chemotherapy-Induced Peripheral Neuropathy. Neurotox Res 2017; 32: 151–162. https://doi.org/10.1007/s12640-017-9729-6
[192] MIYAMOTO T, HIRAMOTO S, KANTO A, TSUBOTA M, FUJITANI M et al. Estrogen decline is a risk factor for paclitaxel-induced peripheral neuropathy: Clinical evidence supported by a preclinical study. J Pharmacol Sci 2021;146: 49–57. https://doi.org/10.1016/j.jphs.2021.03.001
[193] KAWAKAMI K, TUNODA T, TAKIGUCHI T, SHIBATA K, OHTANI T et al. Factors Exacerbating Peripheral Neuropathy Induced by Paclitaxel Plus Carboplatin in Non-small Cell Lung Cancer. Oncol Res 2012; 20: 179–185. https://doi.org/10.3727/096504012X13522227232192

[194] ATTAL N, BOUHASSIRA D, GAUTRON M, VAILLANT JN, MITRY E et al. Thermal hyperalgesia as a marker of oxaliplatin neurotoxicity: A prospective quantified sensory assessment study. Pain 2009; 144: 245–252. https://doi.org/10.1016/j.pain.2009.03.024

[195] DIMOPOULOS MA, MATEOS MV, RICHARDSON PG, SCHLAG R, KHUAGEVA NK et al. Risk factors for, and reversibility of, peripheral neuropathy associated with bortezomib-melphalan-prednisone in newly diagnosed patients with multiple myeloma: subanalysis of the phase 3 VISTA study. Eur J Haematol 2011; 86: 23–31. https://doi.org/10.1111/j.1600-0609.2010.01533.x

[196] KIM SH, CHOI MK, PARK NY, HYUN JW, LEE MY et al. Serum neurofilament light chain levels as a biomarker of neuroaxonal injury and severity of oxaliplatin-induced peripheral neuropathy. Sci Rep 2020; 10: 7995. https://doi.org/10.1038/s41598-020-64511-5

[197] DOLAN ME, EL CHARIF O, WHEELER HE, GAMAZON ER, ARDESHIR-ROUHANI-FARD S et al. Clinical and Genome-Wide Analysis of Cisplatin-Induced Peripheral Neuropathy in Survivors of Adult-Onset Cancer. Clin Cancer Res 2017; 23: 5757–5768. https://doi.org/10.1158/1078-0432.CCR-16-3224

[198] SÁNCHEZ-BARROSO L, APELLANIZ-RUIZ M, GUTIÉRREZ-GUTIÉRREZ G, SANTOS M, ROLDÁN-ROMERO JM et al. Concomitant Medications and Risk of Chemotherapy-Induced Peripheral Neuropathy. Oncologist 2019; 24: e784–e792. https://doi.org/10.1634/theoncologist.2018-0418

[199] LECOMTE T, LANDI B, BEAUNE P, LAURENT-PUIG P, LORIOT MA. Glutathione S-Transferase P1 Polymorphism (Ile105Val) Predicts Cumulative Neuropathy in Patients Receiving Oxaliplatin-Based Chemotherapy. Clin Cancer Res 2006; 12: 3050–3056. https://doi.org/10.1158/1078-0432.CCR-05-2076

[200] MORI Y, KATSUMATA K, TSUCHIDA A, AOKI T. [Single nucleotide polymorphism analysis in the GSTP1 and ABCC2 genes about neuropathy by the Oxaliplatin]. Gan To Kagaku Ryoho 2008; 35: 2377–2381.

[201] DAILY EB, AQUILANTE CL. Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. Pharmacogenomics 2009; 10: 1489–1510. https://doi.org/10.2217/pgs.09.82

[202] QIAN CY, ZHENG Y, WANG Y, CHEN J, LIU JY et al. Associations of genetic polymorphisms of the transporters organic cation transporter 2 (OCT2), multidrug and toxin extrusion 1 (MATE1), and ATP-binding cassette subfamily C member 2 (ABCC2) with platinum-based chemotherapy response and toxicity in non-small cell lung cancer patients. Chin J Cancer 2016; 35: 85. https://doi.org/10.1186/s40880-016-0145-8

[203] SPROWL JA, CIARIMBOLI G, LANCASTER CS, GIOVINAZZO H, GIBSON AA et al. Oxaliplatin-induced neurotoxicity is dependent on the organic cation transporter OCT2. Proc Natl Acad Sci USA 2013; 110: 11199–11204. https://doi.org/10.1073/pnas.1305321110

[204] LOPEZ-LOPEZ E, GUTIERREZ-CAMINO A, ASTIGARRAGA I, NAVAJAS A, ECHEBARRIA-BARONA A et al. Vincristine pharmacokinetics pathway and neurotoxicity during early phases of treatment in pediatric acute lymphoblastic leukemia. Pharmacogenomics 2016; 17: 731–741. https://doi.org/10.2217/pgs-2016-0001

[205] ARGYRIOU AA, CAVALETTI G, ANTONACOPOULOU A, GENAZZANI AA, BRIANI C et al. Voltage-gated sodium channel polymorphisms play a pivotal role in the development of oxaliplatin-induced peripheral neurotoxicity: Results from a prospective multicenter study: SCNA Polymorphisms and OXA Neurotoxicity. Cancer 2013; 119: 3570–3577. https://doi.org/10.1002/cncr.28234

[206] SERENO M, GUTIÉRREZ-GUTIÉRREZ G, RUBIO JM, APELLÁNIZ-RUIZ M, SÁNCHEZ-BARROSO L et al. Genetic polymorphisms of SCN9A are associated with oxaliplatin-induced neuropathy. BMC Cancer 2017; 17: 63. https://doi.org/10.1186/s12885-016-3031-5

[207] TANABE Y, SHIRAISHI S, HASHIMOTO K, IKEDA K, NISHIZAWA D et al. Taxane-induced sensory peripheral neuropathy is associated with an SCN9A single nucleotide polymorphism in Japanese patients. BMC Cancer 2020; 20: 325. https://doi.org/10.1186/s12885-020-06834-0

[208] VAN DEVENTER H, BERNARD S. Use of Gabapentin to Treat Taxane-Induced Myalgias. J Cancer Oncol 1999; 17: 434a–434a. https://doi.org/10.1200/JCO.1999.17.1.434a

[209] RAO RD, FLYNN PJ, SLOAN JA, WONG GY, NOVOTNY P et al. Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: A phase 3 randomized, double-blind, placebo-controlled trial, N01C3. Cancer 2008; 112: 2802–2808. https://doi.org/10.1002/cncr.23482

[210] VON DELIUS S, ECKEL F, WAGENPFEIL S, MAYR M, STOCK K et al. Carbamazepine for prevention of oxaliplatin-related neurotoxicity in patients with advanced colorectal cancer: Final results of a randomised, controlled, multicenter phase II study. Invest New Drugs 2006; 25: 173–180. https://doi.org/10.1007/s10637-006-9010-y

[211] HURLEY RW, CHATTERJEA D, ROSE FENG M, TAYLOR CP, HAMMOND DL. Gabapentin and Pregabalin Can Interact Synergistically with Naproxen to Produce Antihyperalgesia. Anesthesiology 2002; 97: 1263–1273. https://doi.org/10.1097/00000542-200211000-00033

[212] MA Y, LIU W, LIANG L, YE J, HUANG C et al. Synergistic Antinociceptive Effects of Indomethacin–Pregabalin and Meloxicam–Pregabalin in Paclitaxel-Induced Neuropathic Pain. Biomedicines 2022; 10: 1413. https://doi.org/10.3390/biomedicines10061413

[213] MEIER T, WASNER G, FAUST M, KUNTZER T, OCHSNER F et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. Pain 2003; 106: 151–158. https://doi.org/10.1016/S0304-3959(03)00317-8

[214] CHEVILLE AL, SLOAN JA, NORTHFELT DW, JILLELLA AP, WONG GY et al. Use of a lidocaine patch in the management of postsurgical neuropathic pain in patients with cancer: a phase III double-blind crossover study (N01CB). Support Care Cancer 2009; 17: 451–460. https://doi.org/10.1007/s00520-008-0542-x