Neurotherapeutics (2021) 18:2384–2396
https://doi.org/10.1007/s13311-021-01142-2

CURRENT PERSPECTIVES

Chemotherapy-Induced Peripheral Neuropathy: Mechanisms and Therapeutic Avenues

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Accepted: 9 October 2021 / Published online: 21 October 2021

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a serious and often persistent adverse consequence of certain chemotherapeutic agents. It is a major dose-limiting factor of many first-line chemotherapies, affecting 20–50% of patients at standard doses and nearly all patients at high doses. As cancer survivorship continues to increase with improvements in early diagnosis and treatment, more patients will experience CIPN despite completing cancer treatment, which interferes with recovery, leading to chronic pain and worsening quality of life. The National Cancer Institute has identified CIPN as a priority in translational research. To date, there are no FDA-approved drugs for preventing or treating CIPN, with emerging debate on mechanisms and promising new targets. This review highlights current literature and suggests novel approaches to CIPN based on proposed mechanisms of action that aim either to confer neuroprotection against chemotherapy-induced neurotoxicity or reverse the downstream effects of painful neuropathy.

Keywords Chemotherapy-induced peripheral neuropathy · Mechanisms · Treatment · Neuroprotective · Antinociceptive

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating complication of several antineoplastic agents, including taxanes (paclitaxel, docetaxel), platinum derivatives (carboplatin, cisplatin, oxaliplatin), vinca alkaloids (vincristine, vinblastine), and proteasome inhibitors (bortezomib) [1, 2]. Taxanes and vinca alkaloids belong to a class of microtubule inhibitors [3]. Taxanes stabilize microtubules, so they cannot depolymerize and function properly, leading to cell cycle arrest, whereas vinca alkaloids inhibit β-tubulin polymerization, preventing mitotic spindle formation, leading to mitotic arrest and cell death by apoptosis [3]. A recent study demonstrated that integrins, cell surface receptors that mediate cell-extracellular matrix interaction, protect against paclitaxel-induced neuropathy. Paclitaxel exposure altered the branching pattern of nociceptive neurons in *Drosophila* — integrin overexpression rescued compromised interaction between sensory neurons and the extracellular matrix and restored lost nocifensive escape behavior to thermal noxious stimuli [4].

Platinum-based chemotherapies, or "alkylating-like agents" due to their similarity in mechanism to classical alkylating agents, cross-link DNA and form interstrand DNA-platinum adducts, leading to non-specific cell cycle arrest [5]. Bortezomib, a proteasome inhibitor and first-line treatment for multiple myeloma, inhibits the proteasome-ubiquitination pathway, preventing degradation of pro-apoptotic proteins [5, 6]. At clinically relevant doses, bortezomib alters microtubule stabilization by increasing tubulin polymerization, disrupting axonal transport of mitochondria, and promoting cytotoxicity [7]. In line with the sensory axonopathy associated with bortezomib treatment, multiple studies have shown that bortezomib significantly increases polymerized α-tubulin in the sciatic nerve and dorsal root ganglia of rats [8, 9]. A recent study highlighted the role of delta 2 tubulin, a marker of hyperstable microtubules, in bortezomib-induced axonopathy/loss of axonal transport of mitochondria and found D2 accumulation to be sufficient and necessary in driving this process [10]. For these antineoplastic agents, especially vincristine which has the greatest affinity for tubulin among vinca alkaloids, neurotoxicity is a major dose-limiting complication.

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While CIPN pathophysiology is complex and should not be extrapolated from other peripheral neuropathies (e.g., diabetic neuropathy), signs and symptoms typically manifest in a "glove and stocking" anatomical distribution, simultaneously affecting hands and feet bilaterally, with distal-to-proximal symptom progression [11]. CIPN most commonly presents through sensory changes but motor and autonomic deficits can ensue. Signs and symptoms include evoked or spontaneous pain that ranges from tingling ("pins and needles" sensation) to stabbing or burning pain. Mechanical and cold allodynia (pain from pressure and cold temperature, otherwise innocuous), numbness, and weakness are common characteristics of CIPN [12].

CIPN is sometimes mild and reversible, whereas in other cases, it can be severe and irreversible, interfering with daily activities. CIPN prevalence depends on the chemotherapeutic agent, dosage, and duration. In one meta-analysis, it was found that 68.1% of patients experience CIPN within the first month after chemotherapy, 60.0% at 3 months, and 30.0% at 6 months and beyond (considered chronic CIPN) [13]. However, given the heterogeneity of CIPN risk with no validated clinical biomarkers, it is important to identify risk and protective factors for CIPN to better predict outcomes, understand its etiology and underlying mechanisms, and develop a personalized approach to CIPN prevention and treatment.

Clinical risk factors for developing CIPN include a history of pre-existing neuropathy, comorbidities such as diabetes mellitus, lifestyle factors like smoking, and decreased creatinine clearance [13]. Interestingly, a history of autoimmune disease was found to be associated with reduced risk of CIPN [14]. Predisposing genetic factors include single nucleotide polymorphisms (SNPs) in *FGD4*, a gene associated with hereditary peripheral neuropathy in Charcot-Marie-Tooth disease, and genes involved in dysfunctional receptor activity resulting in neuronal apoptosis and prolonged muscle contraction in patients with CIPN treated with platinum drugs for breast and colon cancer, respectively [15, 16]. These CIPN-associated genetic markers may partly explain common symptoms that patients experience, including altered sensation due to apoptosis in dorsal root ganglion (DRG) sensory neurons and muscle ataxia. Cumulative dosing and infusion timing of the chemotherapeutic agent and SNPs in genes coding for voltage-gated sodium channels and myelinating Schwann cell-associated proteins are additional contributing risk factors related to CIPN mechanisms [17].

Status of Treatments for CIPN

The American Society of Clinical Oncology (ASCO) recently updated their guidelines on CIPN preventive and treatment practices [18]. Several agents that have been investigated lack evidence to support their use as potential therapies. Acetyl-L-carnitine was strongly discouraged for prevention of CIPN. Other "natural" approaches such as all trans retinoic acid (vitamin A metabolite) and antioxidants like vitamin E and glutathione, omega-3 fatty acids, and calcium magnesium infusions were not recommended as no benefits for CIPN prevention were found. Calmangafodipir, an intravenous contrast agent for magnetic resonance imaging, explored for its superoxide dismutase-like (anti-oxidant) activity, was not recommended [19]. Other chemoprotectants such as nimodipine, a calcium channel blocker, and amifostine, a cytoprotective agent against cisplatin-induced nephrotoxicity, have shown mixed results and are currently not recommended for CIPN [20, 21]. RhuLIF (human recombinant leukemia-inhibiting factor), a member of the cytokine family that includes IL-6, proposed to be neuroprotective against peripheral neuropathy, was ineffective against CIPN in a randomized, double-blind, placebo-controlled phase II clinical trial [22].

Established neuropathic pain treatments include tricyclic antidepressants (TCAs), dual serotonin and norepinephrine reuptake inhibitors (SNRIs), anticonvulsants, and opioid agonists [23]. Of these, only the SNRI duloxetine, which is US Food and Drug Administration (FDA)-approved for treating major depressive disorder and diabetic neuropathy, exhibits moderate efficacy in treating CIPN and is often used clinically at doses from 60 to 120 mg/day [24]. No other intervention in this drug class has shown comparable therapeutic effects with a favorable risk/benefit ratio. The TCA nortriptyline has a good safety profile but did not significantly relieve paresthesia or pain in a phase III randomized, double-blind, crossover trial [25, 26]. However, one clinical advantage to using antidepressants is improvement in mood which can help with overall treatment. Anticonvulsants like gabapentin and pregabalin that block voltage-gated calcium channels and decrease excitatory neurotransmission have conflicting efficacy data, and side effects including somnolence and dizziness. Opioids have many adverse side effects with chronic use and are not considered first-line treatment for neuropathic pain.

In general, a safer and more effective therapeutic approach may involve combination therapy. For example, the combination of morphine and gabapentin reduced neuropathic pain significantly more than either agent alone in a randomized controlled trial [27]. Combination therapy with nortriptyline and gabapentin led to a synergistic effect [28]. More clinical trials investigating combination therapy specific for CIPN are needed. A compounded topical analgesic gel consisting of baclofen (γ-amino-butyric acid [GABA]-B receptor agonist), amitriptyline (TCA), and ketamine (N-methyl-D-aspartate [NMDA] receptor antagonist) has shown mild benefit in treating CIPN symptoms with no signs of systemic toxicity; however, existing data are inconclusive and further research is required [29].

Drug-repositioning studies can help identify new or secondary actions of already-approved drugs, which may prove more efficient than de novo drug development [30]. Many drug candidates for CIPN prevention and treatment can be re-purposed based on their mechanism (e.g., neuronal damage) or by screening chemical libraries to test drugs with unclear actions to identify the mechanism, while also investigating the safety profile of these drugs to prevent further CIPN progression [30].

Proposed Mechanisms of CIPN

Mechanisms by which chemotherapy-induced neurotoxicity translates to CIPN are complex and multifactorial. Suggested mechanisms include transporter-mediated uptake of chemotherapy drug, oxidative stress secondary to mitochondrial damage, microtubule disruption and subsequent loss of axonal transport, axonal degeneration, damage to DRG sensory neurons, abnormal discharge of pain fibers (A δ and C fibers), upregulation of proinflammatory cytokines, changes to ion conductance, and inhibition of growth factors [31, 32]. Neuronal hyperexcitability through altered expression of voltage-gated ion (Na_v^+, K_v^+, Ca_v^{2+}) channels and transient receptor potential (TRP) channels have also been implicated in CIPN [33]. Notably, axonal degeneration (i.e., Wallerian degeneration, now termed programmed axon degeneration) plays a major role in pathogenesis of many neurodegenerative disorders, including chemotherapy-induced peripheral neuropathy. A "dying-back" axon degeneration mechanism resulting from fragmentation of the distal axon, likely due to some injury or insult such as chemotherapy, has been well-described [34].

While we refer to "CIPN, chemotherapy-induced peripheral neuropathy" throughout this review, we do not exclude changes within the central nervous system. For instance, glial cell (astrocyte) activation measured in nociceptive signaling centers such as the ventrolateral periaqueductal gray and nucleus raphe magnus, as well as in the spinal cord, was observed 21 days post-oxaliplatin in rats [35]. Moreover, central sensitization and nociceptive transmission following spinal application of oxaliplatin (6.6 nM) were detected in the CNS of treated rats [36].

Here, we discuss biochemical pathways related to CIPN and novel targets beyond conventional neuropathic pain treatment and their assignment to neuroprotectant (upstream) vs. antinociceptive (downstream) effects. Table 1 summarizes these mechanisms and potential therapeutic approaches.

Neuroprotective Strategies

Neuroprotective agents are defined as interventions that reverse or delay neuronal damage from further pathological progression or prevent cell death by inhibiting biochemical and metabolic pathways that result in irreversible cell injury. Mechanisms of cellular injury related to CIPN include axon degeneration, dysregulation of calcium homeostasis, mitochondrial damage, and reactive oxygen species formation initiated by several factors (e.g., DNA damage from chemotherapy).

Targeting Programmed Axon Degeneration in CIPN

Axonal degeneration is a well-described hallmark of CIPN [37]. Many CIPN animal models have identified chemotherapy exposure-related retrograde degeneration following distal fragmentation of sensory axons. A large body of preclinical work dedicated to identifying and targeting SARM1, a necessary key driver of Wallerian degeneration following injury, and other models of peripheral neuropathy, through pharmacological small molecule inhibitors and knockout mice, have shown to prevent neuropathic pain and the loss of distal sensory axon endings from vincristine, cisplatin, bortezomib, and paclitaxel-induced neuropathy [38–40]. Studies have also identified NMNAT2, an axon survival factor, as a major regulator of this process when SARM1 is present; efforts have been made to preserve NMNAT2 function and its expression after it was shown that loss-of-function mutations to NMNAT2 in heterozygote and homozygous mice compromised axon function and morphology and triggered axonal degeneration [41].

Restoring Mitochondrial Function via Calcium Homeostasis

Dysregulation of calcium homeostasis secondary to mitochondrial dysfunction is associated with paclitaxel- and vincristine-induced peripheral neuropathy and bortezomib cytotoxicity [42, 43]. Calcium influx is a hallmark of cellular injury. Dysregulation of intracellular calcium is implicated in bortezomib-induced apoptosis via a caspase activation mechanism [43]. Voltage-gated calcium channels have been targets of multiple studies for pain modulation due to their role in neuronal excitability in DRG sensory neurons. In a rodent model of paclitaxel CIPN, a novel drug inhibitor of N-type voltage-gated calcium channels, IPPQ (quinazoline analog), reversed mechanical allodynia and thermal hyperalgesia without impairing motor function or producing rewarding behavior [44]. In another study, ethosuximide, an inhibitor of T-type voltage-gated calcium channels, reversed allodynia and hyperalgesia in a rodent model of paclitaxel and vincristine CIPN; however, ethosuximide failed to produce analgesic effects in a randomized clinical

Table 1 Neuroprotective and antinociceptive strategies for targeting CIPN

Mechanism		Drug/Target examples	Effects	References
Neuroprotective strategies	• Mitochondrial dysfunction and disruption of calcium homeostasis	• Inhibitor of N-type and T-type voltage-gated calcium channels	• Reversal of paclitaxel-induced neuropathy	[44–47]
	• Oxidative stress	• A3 adenosine receptor agonist	• Decreased NADPH oxidase and mechanical allodynia in a paclitaxel-induced CIPN rat model	[49]
		• PPAR nuclear hormone receptor family	• Increased antioxidant activity of enzymes, superoxide dismutase, and catalase	[50–53]
		• APE1/Ref-1 base excision repair	• Increased anti-tumor activity and neuroprotection against platinum-induced CIPN	[54]
	• Activation of immune system and cytokines	• Inhibitors of pro-inflammatory cytokines TNF-α, IL-1, IL-6, IL-8	• Reversal of paclitaxel-induced neuropathy and microtubule destabilization	[57–62]
	• Increased activity of signaling pathways	• AMPK activators, inhibitor of mTOR and MAPK signaling pathways	• Prevention of paclitaxel and cisplatin-induced mechanical hypersensitivity	[63, 64]
		• Angiotensin II (type 1) antagonist	• Reversal of vincristine-induced tactile allodynia, decreased paclitaxel-induced neuropathy	[68, 69]
	• Axonal degeneration	• Inhibition of HDAC6 and nicotinamide mononucleotide (NMN)	• Decreased CIPN and promotion of microtubule stabilization and mitochondrial transport	[72, 73]
		• Inhibition of SARM1	• Prevent CIPN by targeting Wallerian degeneration	[39, 40]
Antinociceptive strategies	• Changes in activity of neurotransmitters and transporters	• Serotonergic agents: duloxetine and topical (10%) amitriptyline (SNRIs)	• Decreased CIPN	[24, 81]
		• Inhibition of glutamate release	• Restored nerve conduction and bortezomib-induced mechanical hyperalgesia. Decreased vincristine- and oxaliplatin-induced CIPN	[86–95]
	• Abnormal discharge of pain fibers (Aδ and C fibers) and increased nociceptive signaling	• Cannabidiol analog	• Reduced paclitaxel-induced mechanical allodynia	[85, 86]
		• FAAH and MAGL, hydrolytic enzymes of endocannabinoids	• Decreased spontaneous discharge of pain fibers and attenuation of paclitaxel-induced CIPN	[106–109]
		• Non-psychotropic CB2 cannabinoid receptor agonist	Analgesic for paclitaxel-induced allodynia	[110, 111]
	• Neuronal hyperexcitability through TRP superfamily, voltage-gated sodium channels, and nicotinic acetylcholine receptors (nAChRs)	• Modulators of TRPA1, TRPM8, TRPV1, TRPV4	• Reversal of taxol, bortezomib, oxaliplatin-induced CIPN	[114–118]
		• Blockade of voltage-gated sodium channels (NaV 1.7, NaV 1.8, NaV 1.9)	• Reversal of CIPN through pharmacological blockade	[125–128]
		• Selective α9α10 nAChR subtype antagonist and α7 nAChR subtype agonist	• Prevention of oxaliplatin-induced CIPN	[119, 120]

trial and, due to excess adverse events, the study was stopped prematurely [45, 46]. Another novel T-type inhibitor, 5bk, reversed mechanical allodynia in a rodent model with paclitaxel-induced pain without binding to opioid receptors [47]. More clinical trials are needed to determine whether these successful outcomes from animal studies can translate to efficacy in humans despite a subjective and more complex measure of pain.

Reducing Oxidative Stress

Reactive oxygen species (ROS) are a normal physiologic consequence of aerobic metabolism but, under uncontrolled pathologic conditions, have deleterious effects on lipids, proteins, and DNA leading to loss of structural, cellular, and biochemical function. Paclitaxel exposure has been associated with increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, upregulating peroxynitrite, an oxidant species produced from the reaction of nitric oxide with a superoxide anion radical, that plays a significant role in cytotoxicity, oxidative injury, and inducing apoptosis and necrosis at high concentrations [48]. In an animal model of paclitaxel-induced neuropathic pain, IB-MECA, an A_3 adenosine receptor agonist, blocked NADPH oxidase activation and redox-mediated pro-inflammatory pathways, reversing mechanical allodynia in paclitaxel-treated rats [49].

Peroxisome proliferator-activated receptors (PPARα, PPARγ, PPARβ/δ) are a group of nuclear hormone receptors that modify gene transcription [50]. PPARγ agonists (thiazolidinediones, or TZDs) are emerging as therapeutic agents for neurodegenerative disorders, demyelinating diseases, cerebral ischemia, and traumatic injury [51]. In a recent study, cotreatment with pioglitazone, a PPARγ agonist that is FDA-approved to treat type 2 diabetes, and cisplatin reduced mechanical and cold hyperalgesia in mice by blocking oxidative stress through increased activity of free radical inactivation enzymes — superoxide dismutase (SOD) and catalase [52]. Another PPARγ agonist, rosiglitazone, achieved effects similar to pioglitazone in oxaliplatin-induced hyperalgesia [53]. However, due to concern that rosiglitazone increases risk for heart attacks, it was removed from the market in many countries but remains FDA-approved for type 2 diabetes mellitus in the United States. Nonetheless, these studies put forth PPARγ agonists as potential CIPN therapeutics by intervening in oxidative stress-related cellular injury.

In response to oxidative DNA damage from chemotherapy agents, the base excision repair process is augmented to remove damaged bases. APE1/Ref-1 (apurinic/apyrimidinic endonuclease 1/reduction–oxidation factor 1) mediates this repair process, while participating in activation of transcription factors that block inflammation [54]. APX3330, a small molecule modifier of APE1 redox function, awaits phase II clinical trials, and APX2009, a small molecule inhibitor of APE1 (although seemingly counterintuitive, enhances DNA repair and stability through redox inhibition), significantly increased anti-tumor activity and neuroprotection against platinum-induced injury [54]. In vivo analysis of oxidative stress (measured by increases in the protein oxidative and lipoperoxidative products, carbonylated protein, and thiobarbituric acid, respectively), was seen in the plasma, sciatic nerves, and lumbar spinal cord of oxaliplatin-treated rats. Administration of silibrin, an antioxidant compound, together with oxaliplatin for 20 days, prevented oxidative stress-induced damage — further strengthening the role of oxidative stress in the setting of chemotherapy-induced peripheral and central neuropathy [55].

Downregulating Immune and Proinflammatory Processes

Chemotherapeutic agents have been found to activate innate and adaptive immune responses partly by activating Toll-like receptors which upregulate NF-kB, a nuclear transcription factor that activates immune response genes, in addition to releasing the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), IL-1, IL-6, and chemokines such as IL-8 [56]. These inflammatory cytokines can directly sensitize A and C fibers, leading to abnormal spontaneous discharge observed in paclitaxel-, oxaliplatin-, vincristine-, and bortezomib-induced peripheral neuropathy [57, 58]. In one study, inhibiting IL-8 signaling through chemokine receptors CXCR1/CXCR2 by the novel drug reparixin reversed paclitaxel-induced peripheral neuropathy in rats and suppressed acetylation of alpha-tubulin (indicating rescue of microtubule destabilization) in vitro [59]. Reparixin has also been tested for its antitumor effects in CXCR1-positive breast cancer but was notably more efficacious for decreasing severity of paclitaxel-induced peripheral neuropathy in a phase Ia clinical trial [60]. Furthermore, anti-inflammatory cytokines like IL-10 have been identified as necessary for resolution of CIPN, seen through the delayed recovery in IL-10 knockout mice with re-introduction of IL-10 decreasing paclitaxel-induced hyperexcitability in DRG sensory neurons [61]. Blockade of IL-1 release in a CIPN rat model significantly reduced vincristine-induced mechanical allodynia [62].

Signaling Pathways

Recently, there have been advances in elucidating the molecular pathophysiology of CIPN. Rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) are signaling pathways involved in the development of CIPN, and inhibiting these signal transduction pathways has emerged as a therapeutic target in neuropathic pain [63]. AMP-activating protein kinase (AMPK) is an inhibitor of mTOR and MAPK signaling [64]. Narciclasine and metformin, both indirect

AMPK activators, have been shown to prevent paclitaxel- and cisplatin-induced mechanical hypersensitivity in mice, with metformin restoring loss of peripheral nerve fibers [64, 65].

Angiotensin II, an endogenous peptide hormone that regulates blood pressure and fluid homeostasis in the renin–angiotensin–aldosterone system, has also been implicated in promoting inflammation and mediating oxidative stress toxicity and aging [66]. Targeting the angiotensin II receptor as a neuroprotective strategy has been studied extensively in recent years, particularly against ischemic insult and traumatic brain injury. Here, we review modulators of angiotensin II with regard to CIPN. In a mouse model of vincristine-induced neuropathic pain, treatment with candesartan, an angiotensin II type 1 receptor (AT_1R) antagonist traditionally used as an antihypertensive drug, coadministered with compound 21 (C21), a selective angiotensin II type 2 receptor (AT_2R) agonist, together reversed tactile allodynia [67]. Past studies of AT_2R agonists have mainly focused on restoring CNS function. However, C21 also restored vincristine-induced loss of myelinated nerve fibers, an indication of peripheral nervous system regeneration. These neuroprotective effects were reversed in AT_2R knockout mice. Candesartan also decreased glutamate levels following induced retinal ischemic and reperfusion injury, suggesting a role in attenuating glutamate-mediated neurotoxicity [68]. In a recent study, losartan, an AT_1R antagonist, significantly delayed paclitaxel-induced neuropathic pain in rats and decreased levels of proinflammatory cytokines IL-1 and TNF-α [69]. Additionally, glucocorticoid receptor and sigma-1 receptor signaling have been identified to be involved in CIPN and may be additional pharmacological targets for treatment of CIPN [70, 71].

Restoring Microtubule Stability and Axonal Degeneration

Histone deacetylase 6 (HDAC6) has been shown to disrupt microtubule stabilization and α-tubulin-dependent mitochondrial transport in vitro and to promote CIPN in vivo. A highly selective HDAC6 inhibitor reversed cisplatin-induced injury and peripheral neuropathy while restoring intra-epidermal nerve fibers [72]. A recent paper highlighted the role of nicotinamide mononucleotide (NMN), a precursor of NAD+, as a mediator of CIPN-induced axonal degeneration; pharmacological bypass of NMN has showed success in mitigating vincristine-mediated degeneration [73].

Neuronal Uptake Transporters

Chemotherapy drugs are transported across cell membranes by organic anion transporting polypeptides (OATPs) and organic cation transporters (OCTs) [74]. Taxanes more commonly use OATPs, whereas platinum derivatives use OCTs; however, both mediate neuronal damage of DRG sensory neurons. Knockout of OATP1B2 ($OATP1B2^{-/-}$ mice) and nilotinib (inhibitor of tyrosine kinase and the OATP1B-type transporter) protected against paclitaxel-induced neuropathy without compromising chemotherapy efficacy [75]. An ongoing clinical trial (NCT04205903) is evaluating the tyrosine kinase inhibitor, nilotinib, for patients with stage I–III breast cancer [76].

Antinociceptive Strategies

In contrast to neuroprotective agents discussed above that work upstream to intervene early in cellular injury processes that result in CIPN, antinociceptive strategies include interventions that modulate processing and interpretation of nociceptive stimulation. Neurotransmitters like serotonin, norepinephrine, glutamate, and substance P are well-known to modulate nociceptive signaling [77]. Changes to these neurotransmitters following chemotherapy treatment have been associated with CIPN in numerous studies [78, 79]. In this section, we discuss novel therapies targeting these neurotransmitters and ion channels/receptors that mediate and transduce pain signals.

Serotonergic Agents

Serotonin is a key CNS neurotransmitter involved in the descending modulatory circuit of nociceptive transmission. As duloxetine is a dual SNRI, it likely acts via this pathway to enhance analgesia (but is not neuroprotective). Use of amitriptyline, another SNRI (formerly a first-line antidepressant), has shifted towards treating fibromyalgia, migraines, and neuropathic pain (notably diabetic neuropathy); its analgesic properties are partly due to its ability to inhibit voltage-gated sodium channels, thereby blocking action potentials and spontaneous discharge of pain fibers [80]. In a non-placebo-controlled pilot study, topical application of high-concentration (10%) amitriptyline cream provided local relief of CIPN and was well-tolerated by participants [81].

Various studies have examined other serotonergic agents. Neurotensin, an endogenous neuropeptide and hormone with various functions — one of which, interacting with norepinephrine, dopamine, and serotonin-secreting neurons — was studied in a rodent model of cisplatin CIPN. The neurotensin receptor 1 agonist (NTSR1), PD149163, significantly improved cisplatin-induced mechanical allodynia in rats; dihydroergocristine, a non-selective serotonin receptor antagonist, blocked the effects of PD149163 [82]. Although neurotensin has been studied as an analgesic in various neuropathic pain models, a recent paper highlighted that neurotensin plays an oncogenic role in digestive cancers [83]. Given the potential for neurotensin to further augment CIPN, it is important to reevaluate its use as a safe therapeutic,

perhaps more appropriately as a therapeutic target or diagnostic marker for digestive cancers that, in turn, could prevent CIPN. In a separate study, serotonin 5HT-2A receptors (5HT-2AR) were shown to be involved in vincristine-induced neuropathy. Administering a 5HT-2AR antagonist significantly decreased vincristine-induced neuropathy and 5HT-$2A^{-/-}$ knockout mice did not develop CIPN in contrast to wild-type 5HT-$2A^{+/+}$ mice [84].

Glutamate

Increased levels of glutamate have been associated with CIPN. Glutamate, the most abundant excitatory neurotransmitter in the CNS and a primary pain neurotransmitter, acts on the NMDA receptor and can sensitize neurons (i.e., neuronal hyperexcitability), increase nociceptive signaling, and subjective pain [85]. Blocking production of glutamate by inhibiting glutamate carboxypeptidase (an enzyme that hydrolyzes *N*-acetyl-aspartyl-glutamate into *N*-acetyl-aspartyl and glutamate) significantly improved nerve conduction velocity that was diminished following cisplatin, paclitaxel, and bortezomib treatment in rats, restoring the loss of sensory conduction often seen with peripheral neuropathy [86]. In another study, bortezomib-treated rats exhibited significantly higher glutamate levels and hyperalgesia compared to control animals, and treatment with the metabotropic glutamate receptor 5 (mGluR5) antagonist MPEP reversed mechanical hyperalgesia to baseline values [87].

Downregulation of glutamate transporters (e.g., GLT-1), which remove glutamate from the synaptic cleft, has been observed in taxol-treated rats that manifest mechanical hyperalgesia [58, 88]. In a recent study, administration of ceftriaxone, a β-lactam antibiotic that upregulates astrocytic GLT-1 expression, significantly improved mechanical allodynia in oxaliplatin-treated mice [89]. Further, memantine, an NDMA receptor antagonist used for treatment of Alzheimer's disease, significantly increased pain threshold at 10 mg/kg in a vincristine CIPN rodent model [90]. An ongoing clinical trial (NCT03709888) is investigating the efficacy of pregabalin and extended-release memantine combination therapy for CIPN [91]. Riluzole, FDA-approved for treating amyotrophic lateral sclerosis, acts on several ion channels including TRPM8 (menthol receptor) which facilitates entry of Na^+ and Ca^{2+} and modulates glutamate activity through suppression of glutamate increase and mechanical allodynia following oxaliplatin treatment [92]. Currently, a randomized, placebo-controlled, double-blind phase II clinical trial (NCT03722680) is evaluating riluzole as a candidate for treating CIPN [93]. Suppressing glutamate excitotoxicity and neuronal sensitization by antagonizing glutamate receptors or blocking glutamate production is a promising novel therapeutic approach for CIPN. Lastly, potentiation of excitatory signaling through glutamate release and extended aberrant ion conductance, under pathological and dysregulated conditions, is mediated in part by pannexin 1 (Panx1) — a large-pore forming channel opened by ATP and glutamate expressed throughout the body including neurons and glial cells [94]. Of the ATP-gated P2X receptor family, modulation of the P2X7 receptor subtype through selective antagonists, pannexin 1 inhibitors, reversed neuropathic pain by blocking glutamate release from nerve terminals in the cerebral cortex of oxaliplatin-treated rats [95].

Cannabinoids

The endocannabinoid system has been investigated for its role in various types of pain including CIPN and offers several molecular targets that could be antinociceptive [96, 97]. Cannabidiol (FDA-approved for rare pediatric seizure disorders) has multiple mechanisms of antinociceptive action within and beyond the endocannabinoid system, including reuptake inhibition of anandamide and adenosine, FAAH inhibition, allosteric modulator at CB_2 receptors and at *mu*- and *delta*-opioid receptors, antagonist at GPR55 (orphan cannabinoid) receptors, TRPV1 agonist, $5HT_{1A}$ agonist, and PPARα agonist [98–102]. Notably, CBD and a more target-selective structural analog, KLS-13019, were shown to reduce paclitaxel-induced mechanical allodynia, mediated partly through $5HT_{1A}$ (but not CB_1 or CB_2) receptors and the mitochondrial Na^+ Ca^{2+} exchanger-1, in a mouse model of CIPN [103, 104].

Preliminary evidence also suggests that other cannabinoids could be useful for treating CIPN [105]. These include inhibition of fatty acid amide hydrolase (FAAH) that slows anandamide breakdown which has shown to decrease spontaneous firing of C-fibers and increase pain thresholds in response to mechanical stimuli in cisplatin-treated mice, as well as combination treatment with CB_1 and delta-opioid receptor agonists significantly attenuating paclitaxel CIPN in animal models [106, 107]. Monoacylglycerol lipase (MAGL) is the primary hydrolytic enzyme of 2-arachidonoyl-glycerol. In one study, MAGL inhibitors reversed paclitaxel-induced allodynia in mice but produced rewarding behavior [108]. In a separate study, an irreversible MAGL inhibitor reversed cisplatin-induced mechanical and cold allodynia, whereas gabapentin and amitriptyline only partly or unsuccessfully reversed neuropathy, respectively [109]. Non-psychoactive CB_2 receptor agonists have been extensively studied in various pain models for treatment of acute and chronic pain, advantageous by providing analgesia without producing CNS side effects [110]. A synthetic CB_2-selective agonist, MDA7, was shown to prevent paclitaxel-induced allodynia while dampening the activity of immune system receptors (e.g., Toll-like receptors), microglia, and proinflammatory cytokines; this effect was reversed with CB_2 antagonists [111].

Transient Receptor Potential Channels

Transient receptor potential (TRP) channels have been implicated in neurodegenerative disease, nociception, and more recently, CIPN [112]. Among the TRP superfamily of calcium-permeable channels, TRPA1, TRPM8, TRPV1, and TRPV4 play a crucial role in the development of neuropathic pain by primary afferent sensitization [112, 113]. For example, antisense oligodeoxynucleotides to TRPV4 (which reduce TRPV4 expression) reversed taxol-induced mechanical hyperalgesia in rats while blocking TRPA1 signaling, necessary for bortezomib- and oxaliplatin-mediated peripheral neuropathy, prevented hypersensitivity [114, 115].

Capsaicin is a high-affinity agonist that acts on TRPV1 (TRP cation channel subfamily V member/vanilloid receptor 1) [116]. In a recent study, application of an 8% (179 mg) capsaicin patch significantly improved CIPN and restored intra-epidermal nerve fiber loss seen at baseline (pre-treatment) when measured post-treatment with skin biopsy — the mechanism is unclear but suggested to be due to prolonged application desensitizing sensory nerves and hence, providing analgesic relief [117].

In one early-phase clinical study, treatment with topical menthol (1%), a TRPM8 agonist, in patients with painful neuropathy, the majority having CIPN origin, provided analgesia while improving mood, catastrophizing, and walking ability [118]. Although our discussion of pharmacological interventions for CIPN has focused on drugs with systemic effects, peripheral treatment can confer advantage to targeted areas of localized pain (tingling, burning, numbness), avoiding first-pass metabolism due to poor bioavailability as well as undesirable side effects.

Nicotinic Acetylcholine Receptors (nAChRs)

The nicotinic acetylcholine receptor (nAChR) has shown to be a therapeutic target for CIPN. In a CIPN animal model, RgIA4, an analog of the α-conotoxin RgIA peptide and selective antagonist of the α9α10 nAChR subtype, prevented oxaliplatin-induced cold allodynia and increased threshold to mechanical hyperalgesia [119]. In addition, multiple doses of RgIA4 produced gradual and sustained pain relief in contrast to tolerance development seen with opioid treatment. Further involvement of nAChRs has shown to mediate CIPN pathology. Stimulation of the homomeric α7 nAChR subtype by selective agonists demonstrated significant reduction of pain threshold to cold stimuli 21 days post-oxaliplatin treatment in rats and prevented painful neuropathy provoked by mechanical and thermal stimuli [120].

Voltage-Gated Sodium Channels (Na_V 1.7, Na_V 1.8, Na_V 1.9)

Voltage-gated sodium channels, especially $Na_V1.7$, $Na_V1.8$, $Na_V1.9$, have been associated with neuronal excitability and transduction of nociceptive signals [121]. Moreover, increased voltage-gated sodium channel activity has been identified in many types of cancer, and voltage-gated sodium channel polymorphisms have been associated with incidence of oxaliplatin-induced peripheral neurotoxicity [122–124]. Pharmacological blockade of these sodium channels that are preferentially expressed in the peripheral nervous system rather than the CNS has shown potential in relieving pain in various experimental models while avoiding psychotropic and other adverse effects [125]. Gain-of-function mutations in $Na_V1.7$ have been associated with paclitaxel-induced neuropathy and selective downregulation of $Na_V1.7$ has shown promising therapeutic relief in animal models [126, 127]. Dexpramipexole, a selective inhibitor of $Na_V1.8$, provided significant analgesia in a mice model of oxaliplatin-induced neuropathic pain and other $Na_V1.8$ blockers have shown efficacy in treating neuropathic pain with phase II trials underway [128]. $Na_V1.9$ blockers have been difficult to develop due to challenges in generating the subtype recombinantly.

Discussion

With increases in cancer survivorship attributable to improved treatments, CIPN is a growing concern because it adversely affects quality of life in many patients. Presently, there is no FDA-approved drug for preventing or treating CIPN. Duloxetine is the only ASCO-recommended drug; however, not all patients benefit from duloxetine (e.g., its analgesic efficacy is better against platinum derivatives than taxanes), and the heterogeneous mechanisms by which chemotherapy agents produce toxicity increases the complexity of CIPN treatment [24]. Establishing which pathways may be necessary versus sufficient in the prevention and progression of CIPN can help us identify targets despite heterogeneous mechanisms.

Herein, we identified novel therapeutics from research literature according to whether these agents intervene in cellular injury processes that contribute to the development of CIPN (e.g., mitochondrial dysfunction and release of inflammatory cytokines) versus those that modify the processing of (chemotherapy-induced) pain signaling. While we have focused on pharmacological intervention, invasive neuromodulation therapy like spinal cord stimulation and non-invasive techniques such as repetitive transcranial magnetic stimulation (rTMS) or exercise may be lower-risk practical strategies for treating CIPN alone or in combined pain management [129, 130]. Complementary approaches through herbal medicine such as the Astragali radix extract,

derived from the *Astragalus membranaceus* plant as well as glucosinolate and the derived isothiocyanate, sulforaphane, from *Brassicaceae* vegetables have shown to inhibit oxaliplatin-induced neuropathy by way of modulating metabolic activation of astrocytes and microglia and Kv7 channels, respectively [131, 132].

Well-designed, large-scale randomized controlled trials are needed to reliably translate data from rodent models and small pilot studies into evidence-based clinical practice. We advocate separate types of trials for prevention vs. treatment of CIPN. For instance, prevention trials might be undertaken in patients at higher risk for developing CIPN. Such patients might be coadministered a novel putative CIPN preventive agent, referenced against duloxetine (non-inferiority comparison) or placebo (superiority comparison) during chemotherapy. As there is currently no preventive strategy, we believe it would be ethically tenable to conduct a randomized, placebo-controlled trial in this instance. Treatment trials (i.e., enrolling patients who have already developed at least some signs of CIPN) could be similarly conducted, although — based solely on ASCO guidelines, not FDA approval — there would be a stronger ethical motive to include duloxetine as a comparator. Trials should also be designed with the goal of determining whether the agent is neuroprotective vs. antinociceptive, and appropriate biomarkers and clinical signs/symptoms should be monitored at regular intervals pre- and post-treatment to track the time course of symptom and functional severity. A number of design variables are important to consider including sample heterogeneity, confounders, and measurement reliability, which have been summarized elsewhere [133]. Finally, we note that because of our limited understanding of CIPN pathophysiology and its heterogenous presentation, early patient education and discussion with clinicians is needed to alleviate the burden of CIPN and improve quality of life in cancer patients and survivors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13311-021-01142-2.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Declarations

Competing Interests The authors declare no competing interests.

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