Original Article

# New Insights into Potential Prevention and Management Options for Chemotherapy-Induced Peripheral Neuropathy

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## ABSTRACT

**Objective:** Neurological complications such as chemotherapy-induced peripheral neuropathy (CIPN) and neuropathic pain are frequent side effects of neurotoxic chemotherapy agents. An increasing survival rate and frequent administration of adjuvant chemotherapy treatments involving neurotoxic agents makes it imperative that accurate diagnosis, prevention, and treatment of these neurological complications be implemented. **Methods:** A consideration was undertaken of the current options regarding protective and treatment interventions for patients undergoing chemotherapy with neurotoxic chemotherapy agent or experience with CIPN. Current knowledge on the mechanism of action has also been identified. The following databases PubMed, the Cochrane Library, Science Direct, Scopus, EMBASE, MEDLINE, CINAHL, CNKI, and Google Scholar were searched for relevant article retrieval. **Results:** A range of pharmaceutical, nutraceutical, and herbal medicine treatments were identified that either showed efficacy or had some evidence of efficacy. Duloxetine was the most effective pharmaceutical agent for the treatment of CIPN. Vitamin E demonstrated potential for the prevention of cisplatin-IPN. Intravenous glutathione for oxaliplatin, Vitamin B6 for both oxaliplatin and cisplatin, and omega 3 fatty acids for paclitaxel have shown protection for CIPN. Acetyl-L-carnitine may provide some relief as a treatment option. Acupuncture may be of benefit for some patients and Gosha-jinki-gan may be of benefit for protection from adverse effects of oxaliplatin induced peripheral neuropathy. **Conclusions:** Clinicians and researchers acknowledge that there are numerous challenges involved in understanding, preventing, and treating peripheral neuropathy caused by chemotherapeutic agents. New insights into mechanisms of action from chemotherapy agents may facilitate the development of novel preventative and treatment options, thereby enabling medical staff to better support patients by reducing this debilitating side effect.

**Key words:** Bortezomib, chemotherapy-induced peripheral neuropathy, cisplatin, management, neuropathic pain, prevention, taxane, treatment, vincristine

## Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent, dose-limiting side effect resulting from the

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administration of commonly used neurotoxic chemotherapy agents. It is characterized by paresthesia, dysesthesia, impaired movement, and occasionally pain. The most common symptoms reported by patients include sensory symptoms of numbness and tingling, followed by burning, shooting, throbbing, and stabbing feelings. Moreover, patients may experience motor symptoms such as dropping items, splaying fingers, and inability to complete normal daily activities.[1] This side effect is difficult to prevent and control without resorting to dose reduction or cessation of chemotherapy treatment.[2]

Overall, CIPN is considered a serious and significant neurological adverse effect of chemotherapy and must be monitored from presentation as worsening symptoms can occur from the administered treatment. CIPN may be temporary but in a third of cases, it has been found to be a permanent side effect from the chemotherapy treatment employed.[3] There have been numerous studies trialing pharmaceutical agents, nutrients, herbs, and other modalities for the prevention and/or treatment of CIPN. Thus, the objective was to identify the best possible evidence-based options for clinicians that could be of beneficial assistance to patients undergoing chemotherapeutic treatments.

## Methods

The aim of this inquiry was to investigate which efficacious protective and/or treatment options were available for patients undergoing chemotherapy with a neurotoxic chemotherapeutic agent or who experience CIPN. New insights into mechanisms of action from chemotherapeutic agents may highlight new preventative and treatments options that could assist medical staff provide patients with treatment options that could decrease the debilitating burden encountered with the side effects of CIPN. A mini-literature review was conducted for each section.

### *Selection criteria*

The inclusion criteria for each sub-section included:

1. Any type of human clinical trial (e.g., randomized controlled trial [RCT]) or descriptive study, e.g., retrospective studies, case-control studies).
2. Animal studies.
3. The use of a mechanism of action study that administered a pharmaceutical, nutrient(s) or herbal medicine as the main intervention and specifically investigating its effects on reducing the primary outcome, i.e., CIPN, and
4. The journal article or abstract was in English.

### *Databases*

The following databases were used to retrieve journal articles: PubMed, the Cochrane Library, Science Direct, Scopus, EMBASE, MEDLINE, and Google Scholar. Chinese Databases included CNKI and CINAHL.

### *Search terms*

Electronic databases were searched using the following search terms, "CIPN" or "cisplatin" or "taxanes" or "paclitaxel" or "docetaxel" or "oxaliplatin" or "carboplatin" or "platinum compounds" or "proteasome inhibitors" and "peripheral neuropathy" or "CIPN" and "mechanism of action" or "pharmaceutical agent" or "nutrient" or "herb" or "herbal medicines" or "chinese herbal medicines" or "ayurvedic herbal medicines."

### *Risk bias assessment*

The risk bias of both animal and human studies was assessed using the Cochrane risk of bias assessment tool (http://handbook.cochrane.org/,part 2, Chapter 8).

### *Data synthesis*

All human clinical trial data (excluding descriptive studies) was analyzed using RevMan version 5.2.7 (Cochrane Informatics and Knowledge Management Department) to quantify and compare the efficacy outcomes of intervention versus control.

## Results

### *Mechanisms of action for chemotherapy-induced peripheral neuropathy*

The administration of chemotherapeutic agents results in numerous cellular changes including loss of sensory terminals in the skin, alterations of membrane receptors, changes in intracellular signaling, neurotransmissions, excitability, and cellular metabolism. These effects can negatively influence neuronal and glial cell phenotypes which may contribute to the development of CIPN, thus hindering the understanding of specific mechanism underlying this side effect.[4] A recent review by Boyette-Davis *et al.*[4] identified a number of different mechanisms of actions for CIPN [Table 1].

Insight into the mechanisms of action of chemotherapy agents that contribute to CIPN is important when considering agents that may assist in CIPN prevention and treatment. Although research has provided an understanding of the possible mechanisms underlying CIPN, current clinical trials have not reported effective preventative or treatment options. It is also important

**Table 1: Mechanisms of action identified for CIPN**

| Mechanism of action | Explanation | Conclusion |
|---|---|---|
| Genetic influences | Recent review identified a number of studies looking at CIPN genetics[5] however, these results have not be reproducible[4] | Potential to identify patients at increased risk of CIPN. Further research still required |
| Neuronal influences | | |
| Altered activity and expression of voltage-gated ion channels | $Na^+$ entry into a neuron is altered e.g., oxalate from oxaliplatin, leading to altered thresholds and ectopic firing.[6,7] ↑ $Na^+$ ↓ $K^+$ channels<br>$Ca^{++}$ also plays a major role with increased levels of voltage-gated $Ca^{++}$ channel mRNA reported in DRG[8] | Possible protection by use of voltage-gated $K^+$ channel openers e.g. retigabine (mouse study).[9] Administration of voltage-gated $Ca^{++}$ drugs such as gabapentin and ethosuximide may decrease reflex hypersentivity[10,11] |
| Alterations of neurotransmission | Altered serotonin transporters[12]<br>Altered glutamate signaling[13]<br>↓ expression of glutamate transporter GLAST in spinal astrocytes[14,15]<br>Animal models show ↓ spinal mu-opioid receptor activation by endomorphin-1[16]<br>Altered endocannabinoids[17]<br>Possible alterations of A3 adenosine receptors[18] | ↑ clearance of excitatory neurotransmitter glutamate prevents excitotoxicity which may affect CIPN[19]<br>Down regulation of glutamate transporters maybe a common mechanism in CIPN subtypes[4] |
| Alterations of transient receptor potential channels | ↑ TRPV1 expression found in DRG in animal models affecting thermal hypersensitivity[20]<br>Cold sensitivity from oxaliplatin was found to be TRPA1 dependent in animal models[21]<br>Possible modulation of TRPM8 channel may have analgesic effects[22] | TRPA1 was found to activate cold sensitivity in rodents but has not been able to be replicated in humans[23] limiting translational impact<br>Possible involvement with TRPV1, TRPV4 and TRPA1 channels after chemotherapy[24]<br>Topical menthol has been reported for carboplatin-IPN[25] |
| Intracellular signaling pathways | Caspase signaling associated with animal models causing potential neuron apoptosis[26]<br>Erk 1/2 and p38 MAPK are activated by cipslatin and oxaliplatin leading to DRG apoptosis[27] | Targeting caspases may assist in protecting against CIPN development<br>Possible protection by promoting NGF[28] |
| Changes to intracellular structures | Damage to glial and neuronal mitochondria has been a focus[29]<br>↓ expression of APE1 is associated with ↑ nociceptive responding[30]<br>Other organelles damaged include lysosomes and endoplasmic reticulum in neurons and schwann cells[31]<br>↓ axonal transport from paclitaxol and vincristine due to anti-tubinal activity[32,33] plus bortezomib and oxaliplatin[34,35] | APE1 may have a potential protective effect but still needs further research[30]<br>Further research into ↓ axonal transport may prove to have potential protective properties |
| Loss of IENF and MC | Reason for ↓ touch perception[36]<br>Specific mechanism of loss of IENF is unclear[4]<br>↓ CCL2, a chemokine involved in proinflammatory responses in DRG linked with CIPN[37] | Tetracycline derivative, minocycline, prevents IENF loss by reducing neuro-inflammation. In animal models is has shown to be protective for oxaliplatin and palitaxel CIPN[38,39]<br>Interventions to suppress CCL2 has been found to block behavioral signs of CIPN and distal IENF density in rats[37] |
| Glial cell function | Chemotherapy causes cytokine release e.g., TNF-α from schwann, satellite, and astrocyte cells resulting in decreased nerve fibers impairing action potential, DRG neuron apoptosis, and neuropathic pain[40-45]<br>Satellite cells affected by chemotherapy also causes increased gap junction coupling causing an analgesic response in mice[46] | Treatment with minocycline or carbenoxolene can decrease hyperalgesia response in rodents[14] |
| Cytokine and chemokine binding | Chemotherapeutics enhances cytokine release e.g., TNF-α, IL-1β and chemokine e.g., MCP-1 bind to receptors located on neurons and glial cells and increase pain[47]<br>TLR is one receptor known to be involved with CIPN[48]<br>In rats, TLR4 increases palitaxol-induced hyperalgesia<br>MCP-1 receptor CCR2 is altered in CIPN[37] | TLR4 antagonists e.g. a lipopolysaccharides isolated from Rhodobacter sphaeroides has been found to decrease hyperalgesia in rats[49]<br>TLR2 antagonists have also been found to assist cisplatin CIPN[50]<br>CCR2 antagonists decrease neuropathic pain in mice[51] |

CIPN: Chemotherapy-induced peripheral neuropathy, DRG: Dorsal root ganglia, TRPV1: Transient receptor potential vanilloid 1, TRPM8: Transient receptor potential melastatin 8, TRPA1: Transient receptor potential ankyrin 1, MAPK: Mitogen-activated protein kinase, NGF: Nerve growth factor, IENF: Intraepidermal nerve fibers, MC: Meissner's corpuscle, TNF-α: Tumor necrosis factor alpha, IL-1β: Interleukin 1, beta, MCP-1: Monocyte chemoattractant protein-1, TLR: Toll-like receptors, GLAST: Glutamate-aspartate transporter, APE1: Apurinic/apyrimidinic endonuclease 1

when studying the mechanisms of action underlying CIPN development, the validity and reliability of the reported results. From the data identified to date, further research and treatment options are warranted and a redirected focus may needed that examines the role of glial cells and inflammatory pathways in CIPN.

## *Current treatment and prevention options*

Clinical trials investigating pharmaceutical agents and complementary and alternative therapies for the prevention and treatment CIPN were identified. Listed below are the current trials for each agent categorized under individual neurotoxic chemotherapy agent. Due to the comprehensive data acquisition in each category, studies of different levels of evidence have been included in this analysis. The studies included were evaluated using a separate tool, the Australian National health and Medical Research Council's (NHMRC) body of clinical evidence assessment matrix. This is an assessment tool that assigns a level/grade (Level I: Strongest evidence to

**Table 2: Pharmaceutical agents trialed for CIPN**

| Chemotherapy agent | Pharmaceutical agents trialed | Level of evidence | Total number of participants from trials | Recommendations |
|---|---|---|---|---|
| Ciplatin | Amifostine[58-64] | Level III | 657 | Possible ototoxicity protection particularly for children |
| Limited protection for CIPN | | | | |
| Oxaliplatin | Amifostine[65] | Level IIIc | 15 | Possible decrease in severity of CIPN by subcutaneous application |
| | Carbomazepine/oxcarbazepine[66-69] | Level IIIb | 103 | Limited protection noted |
| | Calcium channel blockers[70] | Level IIIb | 116 | Retrospective study found they lowered the incidence for acute CIPN but not chronic |
| Taxanes | Amifostine[61,71,72] | Level III | 98 | Possible protection against severe CIPN development |
| Vincristine | Amifostine[64] | Level IIIa | 97 | No protection noted |
| Carboplatin/taxane | Amifostine[73-77] | Level III | 446 | Possible protection against severe CIPN development |
| | rhuLIF[78] | Level II | 117 | No protection noted |
| CIPN treatment | Gabapentin[79,80] | Level II | 177 | Failed to show any benefit although may decrease pain in some people |
| | Lamotrigine[81] | Level II | 131 | No benefit noted |
| | Pregabalin[57] | Level IIIb | 23 | May decrease the severity of sensory oxaliplatin PN in patients who reach the target dose of 150 mg tds (22%) |
| | Amitriptyline/nortriptyline[82,83] | Level III | 95 | Modest effect on reducing pain |
| | Venlafaxine[54-56] | Level IV | 4 | Possible effect on reducing pain although only case studies |
| | Duloxetine[52,53] | Level II | 232 | Statistically significant in reducing pain from CIPN |

CIPN: Chemotherapy-induced peripheral neuropathy, PN: Peripheral neuropathy

level IV: Weakest evidence) based on the strength of the published study.[1]

## *Pharmaceutical agents*

No pharmaceutical agent has yet been reported to significantly prevent CIPN. Several agents have been found to have a moderate benefit for the treatment of CIPN however, further trials are required. Possible beneficial treatment options for pain associated with CIPN include duloxetine (Cymbalta)[52,53] and other anti-depressants such as venlafaxine (Effexor).[54-56] Currently, pregabalin (Lyrica) has been administered with some benefit for nerve pain although only one open label trial[57] has been conducted with CIPN. Table 2 presents the chemotherapeutical agents and the pharmaceutical agents trialed for each drug, the total number of participants in all the trials conducted on the drug and the outcomes reported.

## *Nutraceutical agents*

Currently, there are no established neuroprotective nutraceuticals or treatment options for CIPN. There are several nutraceuticals which have shown promise for selective neurotoxic chemotherapeutic agents such as Vitamin E with cisplatin,[84-86] intravenous glutathione for oxaliplatin administration,[87,88] Vitamin B6 with hexamethylmelamine,[89] and cisplatin although it was reported to interfere with treatment response rate and omega 3 fatty acids for paclitaxel.[90] Acetyl-L-carnitine has also shown promise as a treatment option for CIPN[91,92] with further research required from large RCTs. Overall, the results with the administration of various nutraceuticals remains inconsistent and further investigations are required to confirm efficacy and safety. Table 3 presents the trials conducted on nutraceuticals with specific chemotherapeutic agents.

## *Herbal medicines*

A number of herbal medicines have shown promise as treatment and preventative agents for CIPN. However, the majority of the journal articles identified were laboratory animal studies ($n$ = 17). Human studies consisted of one multi-center, randomized double-blind placebo-controlled trial, six randomized trials, six retrospective studies, one uncontrolled study, and three case reports [Table 4]. From the Asian herbal combinations, Gosha-jinki-gan (GJG) is the herbal medicine that has been trialed extensively in animal studies and human clinical trials.[120-122,128,129,132-135] There are three retrospective studies used controls for FOLFOX (oxaliplitin, fluorouracil, and leucovorin) and paclitaxel administration,[120,121,128] one RCT[134] comparing Vitamin B12 administration with the herbal combination and a recent Phase II multi-center, randomized, double-blind, placebo-controlled trial conducted as an adjuvant treatment with FOLFOX.[129] All studies concluded that

[1]National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Commonwealth of Australia: National Health and Medical Research Council 2009.

**Table 3: Nutraceuticals agents trialled for CIPN**

| Chemotherapy agent | Nutraceutical trialled | Level of evidence | Total number of participants from trials | Recommendations |
|---|---|---|---|---|
| Cisplatin | Vitamin E[84,86,93] | Level II | 190 | Recommended as an adjunct during treatment to prevent CIPN. Dose 400 mg/day |
| | Glutamine[94] | Level III | 26 | Possible recommendation as it may reduce severity of CIPN. Dose: 2 days consequently with cisplatin |
| | Alpha-Lipoic acid[95] | Level II, Level IIIa | 243 | Not recommended as no protection noted |
| | Glutathione[96-98] | Level II | 244 | Trend toward protection. Dose: 1.5-2.5 g daily |
| | Vitamin B6[89] | Level IIIb | 248 | Prevented CIPN but adversely affected response duration. Dose: 300 mg daily |
| Oxaliplatin | Magnesium/calcium infusions[94,99-104] | Level II | 418 | Conflicting results but is not recommended to use in conjunction with treatment |
| | Vitamin E[105] | Level II | 34 | Not recommended as no differences noted. Dose: 400 mg/day |
| | Alpha-lipoic acid[95,106] | Level III | 15 | Reduced severity of severe CIPN. Dose: 800 mg daily |
| | N-acetyl cysteine[107] | Level IIIa | 14 | Not recommended as no differences noted. Dose: 1200 mg daily |
| | Glutathione[87,89] | Level II, Level IIIb | 79 | Possible protection as one trial had a significant protective effect. Dose: 1500 mg |
| | Glutamine[108] | Level IIIa | 88 | Possible recommendation as it may reduce severity of CIPN. Dose: 15 g twice a day, or IV 20 g for 2 days consequently with oxaliplatin |
| | Vitamin B6[109] | Level II | 23 | Recommended, as it may prevent CIPN |
| Taxanes | Glutamine[110,111] | Level IIIa | 47 | Not recommended as it was not statistically significant Dose: 10 g t.i.d for 4 days after chemotherapy |
| | Acetyl-L-carnitine[112] | Level IIIa | 409 | Not recommended as worsened CIPN in patients taking ALC. Dose: 3000 mg daily |
| | Omega 3 fatty acids[91] | Level IIIa | 69 | Recommended as it showed statistical significance. Dose: 640 mg t.i.d |
| | Vitamin B12[113] | Level IIIb | 1 | Recommended as possible protection. A case study from a trial of 71 people. Dose: 1000 mcg daily |
| Cisplatin/taxol | Vitamin E[99,114] | Level II | 247 | Not recommended but may have possible protection in some patients. Dose: 400 mg/day |
| Bortezomib | Acetyl-L-carnitine[115] | Level II | 19 | Not recommended to be given prophylactically |
| CIPN treatment | Acetyl-L-carnitine[92,93] | Level IV | 51 | May provide improvement of symptoms if administered after chemotherapy cessation. Dose: 1 g t.i.d |
| | Alpha-lipoic acid[116] | Level III | 14 | Improved neurological symptoms. Dose 600 mg IV weekly over 3-5 weeks |

CIPN: Chemotherapy-induced peripheral neuropathy, IV: Intravenous

this herbal combination may provide neuroprotection. Other herbal medicines which showed promise as protective agents include Kieshikajutsubuto[124] and Shakuyaku-Kanzo-to[126] while sweet bee venom may be useful in treating CIPN once it has developed.[130,131]

### *Other therapies*

Acupuncture has shown promise as a treatment option for CIPN. A systemic review was conducted in 2013 examining the effects of acupuncture on the management of CIPN,[136] which identified seven clinical trials and one experimental (rat) study. The limitations identified for these studies included small sample size, poor controls or no controls, poor randomization, and lack of blinding. From this, it can be concluded that while further studies are required, patients with CIPN may benefit from acupuncture.

Another option for clinicians, practitioners, and nurses includes topical application of analgesic agents. A combination of baclofen 10 mg, amitriptyline HCL 40 mg (3%), and ketamine 20 mg (1.5%) in a base of pluronic lecithin organogel and was found to be beneficial for sensory neuropathy over placebo ($P = 0.053$) and decreased motor neuropathy symptoms ($P = 0.021$).[137] However, a Phase III RCT trial on 462 patients with CIPN found no difference in 6 weeks of treatment with 2% ketamine and 4% amitriptyline cream ($P = 0.363$).[138] Recent case studies examining the topical application of menthol (1%) have found it beneficial as a novel analgesic therapy for cancer neuropathic pain.[139] In addition, high dose topical capsaicin cream may show benefit although no studies for CIPN have been conducted.[140]

## Discussion

Despite the incidence of CIPN and the significant impact it has on the effectiveness of chemotherapy due to its dose-limiting effects, there are no current treatment or preventive

**Table 4: Herbal medicines trialled for CIPN**

| Chemotherapy agent | Herbal medicine trialed | Level of evidence | Total number of participants from trials | Recommendations |
|---|---|---|---|---|
| Oxaliplatin | Ginkgo biloba[117] | Level IIIb | 17 | Possible neuroprotection, do not use with patients who are on blood thinning medication including aspirn or on avastin/eribitux |
| | Buyang huanwu[118] | Level II | 84 | Decreased CIPN but information not given. This is a tea that could be drunk through chemotherapy |
| | Geranii herba plus Aconiti radix[119] | Level II | 58 | Was found to decrease neuropathic pain but information not given |
| | GJG[120,121,122,123] | Level II | 238 | Recommended as it had a positive response. Found to have neuroprotective values. However, only available in Japan and certain Asian countries |
| | Kieshikajutsubuto[124] | Level III | 11 | Patients had 76.6% improvement. Recommended |
| | Ogikeishigomotsuto[125] | Level IIIb | 1 | Decreased neuropathic pain but only a case study. Further research needed |
| | Shakuyaku-kanzo-to[126] | Level IV | 44 | 50% responded to this while 65% responded to GJG. Both can be recommended in Asian countries |
| Paciltaxel | Modified Chai Hu Long Gu Mu Li Wan[127] | Level IIIa | 48 | Possible neuroprotection. Worth considering |
| | GJG[128] | Level IIIa | 82 | Possible neuroprotection and better when administered early. Recommended |
| | Shakuyaku-kanzo-to[129] | Level III | 23 | Reduced neuropathic pain. Worth trying as a treatment option |
| Taxol/carboplatin | Sweet bee venom[130,131] | Level IV | 16 | This is a treatment for CIPN and involves injecting into hte acupuncture point. Was found to decrease pain and neuropathy. Requires a qualified and skilled pratitioner to administer for treatment |

CIPN: Chemotherapy-induced peripheral neuropathy, GJG: Goshajinkigan

options with conclusive efficacy and safety data. However, there are a number of possible avenues that would be advantageous to trial in a clinical setting or via clinical research. First, the increased ability for genetic testing may provide a new avenue for clinicians to identify individuals at high risk of developing CIPN outside the known risk factors such as diabetes, alcoholism, HIV, and Vitamin B12 deficiencies.[3] Considering this side effect can directly affect certain patient's professional ability, general physicality, and quality of life, having the ability to offer this service to patients allows the individual to know their changes of developing this side effect. Hence, certain decisions can then be implemented to assist in possible protection or change chemotherapeutic agents if applicable.

The neuronal influences offer the greatest opportunities for protective and treatment options. First, voltage-gated potassium channel openers such as retigabine[9] shows great potential for researchers to conduct a randomized clinical trial to ascertain if this agent does have benefit in preventing CIPN. In addition, the administration of voltage-gated calcium drugs such as gabapentin and ethosuximide may decrease reflex hypersensitivity.[10,11] This has the potential as a treatment option for those patients who are experiencing reflex hypersensitivity postchemotherapy.

Alterations of neurotransmitters involving the down regulation of glutamate transporters may have potential protective benefits. Possible agents that could be considered include phenyl pyrimidine compounds such as the acetylcholinesterase inhibitors used in the treatment of Alzheimer's disease e.g., donepezil, galanathamine, and tacrine.[141] These drugs have been shown to protect neuronal cells and decrease glutamate neurotoxicity. This provides a new avenue for researchers to consider for the protection of CIPN.

Another neuronal influence which shows potential for treatment options includes the alterations of transient receptor potential channels. To date, menthol cream has shown promise as a topical treatment for CIPN particularly for carboplatin,[25] which works via these channels. This may be an easy option for patients to apply topically to alleviate symptoms of CIPN without further ingestive medicine.

Intracellular signaling activity that involves increasing nerve growth factor (NGF) is another option. Although direct administration of NGF has not shown benefit to date in clinical trials on humans due to unwarranted side effects,[142] there are agents that have been found to increase NGF such as Vitamin B12,[143] acetyl-L-carnitine,[144] rosemary,[145] *Polygala tenuifolia* (Ninjin-Yoei-To, Kamp Japanese Herbal),[146] *Codonopsis pilosula*,[147] and *Dioscorea nipponica*.[148] *Dioscorea* in particular has been trialed for diabetic neuropathy and was found to increase neurite

outgrowth, enhance nerve conduction, and exhibit improvement on damaged axons. The fact that it has been found to reverse functional and structural changes and induce neural regeneration may make this herb an excellent candidate for a trial on CIPN.[148]

Changes to intracellular structures are another mechanism of action by which there is an opportunity. APE1 may have a potential protective effect by decreasing axonal transport but still needs further research.[30] Loss of intraepidermal nerve fibers (IENF) and Meissner's corpuscle also gives rise to opportunities. Currently, tetracycline derivatives have not been clinically trialed on humans for CIPN, but derivatives, such as minocycline, has been found to prevent IENF loss by reducing neuro-inflammation. In animal models, it has shown to be protective for oxaliplatin and palitaxel CIPN.[38,39] This may be an agent that researchers and clinicians could trial considering the positive results found in animal models.

Glial cell function is another mechanism which could be targeted. Again treatment with tetracycline derivatives such as minocycline or carbenoxolone has been found to decrease hyperalgesia response in rodents.[14] This may provide another treatment option for clinicians and researchers. Finally, decreasing inflammation could provide protection against CIPN. Nonsteroidal anti-inflammatory agents have not provided a treatment option for people experiencing CIPN as they are not peripherally acting;[149] however that opens the field for other agents that could play a protective role.

A number of nutrients and herbal medicines that have shown potential for protective benefits for CIPN possess anti-inflammatory activity. These include omega 3 fatty acids,[91] Vitamin E,[86] curcumin,[150] chamomile,[151] sweet bee venom,[152,153] and the combination of Asian herbal medicines.[154-157] Further investigations in the anti-inflammatory activity and prevention of CIPN are required.

Currently, no pharmaceutical, neutraceutical, or complementary agent has been found beneficial in preventing or treating CIPN. Based on the data collected, various agents may be suggested although the level of evidence of the studies needs to be recognized. Certain pharmaceutical agents have shown potential for the treatment of CIPN pain as with duloxetine (Cymbalta) and other anti-depressants such as venlafaxine (Effexor) although Effexor was case study based. Pregabalin is the pharmaceutical drug of choice for clinicians at present based on an open label trial. This has been chosen due to lower dose and less side effects compared to gabapentin.

For neutraceuticals, Vitamin E shows potential for prevention of cisplatin-induced ototoxicity, intravenous glutathione for oxaliplatin administration, Vitamin B6 for both oxaliplatin and cisplatin and omega 3 fatty acids for paclitaxel administration. Acetyl-L-carnitine may provide some relief as a treatment option for CIPN after chemotherapy cessation but should not be used as a preventative agent during chemotherapy. Acupuncture may be of benefit for some patients and GJG may be of benefit for protection of oxaliplatin-IPN for patients in Japan. A number of Asian herbs have been found to have possible benefits for treatment and may provide some relief for patients experiencing neuropathic pain from chemotherapy.

The new insights into the mechanism of actions of CIPN may highlight new drugs, nutrients, or herbs that could assist in prevention of this disabling side effect. However currently, there is no gold standard prevention or treatment of CIPN. It is suggested for clinicians, nurses, and other health professionals treating people with CIPN to use composite measurement outcomes including the full complexity of both positive symptoms (pain, paresthesia, and dysethesia) and negative ones (numbness).[158] Trialing potential treatment options such as aceyl-l-carnitine on patients with numbness and dysthesia might be worthwhile. Discussing, identifying, and suggesting interventions with possible protective benefits for patients such as Vitamin E, B12, and omega 3 fatty acids displays best care.

If these interventions do not prevent this side effect, and as there is still no proven prophylactic or therapeutic intervention, patient presentation of CIPN during chemotherapy requires modification or cessation of treatment. This is still the preferred strategy to date for patients. Ultimately, collaboration of health professionals and implementing strategies to prevent side effects such as CIPN give rise to best care benefits for patients which should be the aim for all healthcare practitioners.

## Conclusion

Clinicians and researchers acknowledge that there are numerous challenges involved in understanding, preventing, and treating peripheral neuropathy caused by chemotherapy agents. New insights into mechanisms of action from these chemotherapeutic agents may facilitate the development of novel preventative and treatment options, thereby enabling medical staff to better support patients by reducing this debilitating side effect.

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