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Chemotherapy Induced Peripheral Neuropathy and Therapeutic Options: A Review

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Abstract

Background: *Peripheral neuropathy is characterized by distal damage to neurons along PNS which consists of loss of function. This would result from various factors.*

Chemotherapy Induced Peripheral Neuropathy (CIPN), a side effect of chemotherapy decreasing quality of life. There are various mechanisms by which these cause CIPN are neuronal structural and functional alterations.

Method: *Background searches into peripheral neuropathy and the chemotherapeutic agents that induce CIPN and their mechanisms were done from a series of journal databases.*

Treatment options were sought from the same databases dating between 2003 and 2019. From this the therapeutic options that have been explored and tried and the updates to these have been enumerated a discussed.

Discussion: *CIPN manifests from a heterogenous group of aetiologies. One standardized treatment option is not available for proper treatment of CIPN. Research over the years has produced methods of prevention and treatment for CIPN patients, including the use of preventative therapy, polypharmacy and some specific first line drugs. Nonpharmacological methods of treating CIPN comprises of the recent use of medicinal plants and complementary therapies for severe pain relief and better quality of life for these patients.*

Future Scope of Studies: *Over the past decade, despite many efforts to develop a standardized treatment for CIPN, there has been little success. As a result, many more future studies are strongly indicated.*

Keywords: *Chemotherapy Induced Peripheral Neuropathy, Chemotherapy, Neuralgia, Neuropathy Mechanisms, Peripheral Neuropathy Therapy.*

Introduction

Peripheral neuropathy (PN) – characterized by pain, numbness, and tingling in the extremities and slow nerve conduction – affects a significant percentage of the U. S. population and can be extremely debilitating. The prevalence of peripheral neuropathy in the general population is 2.4% and increases with age to an estimated 8% in those older than 55 years (1), (2). Peripheral neuropathy is more common in patients with diabetes mellitus, human immunodeficiency virus infection, and dysproteinaemic disorders and most importantly in those receiving chemotherapy.

Peripheral neuropathy manifests as axonal degeneration. Diagnosis of PN involves a complete evaluation to determine the extent of the neurological deficit as well as a complete history and physical examination to determine the possible aetiology. Despite thorough history and physical exam, aetiology remains a mystery in approximately 50 percent of cases.

Peripheral neuropathy can be the result of genetics, chronic disease, environmental toxins, alcoholism, nutritional deficiencies, or side effects of certain medications, for instance chemotherapeutic agents.

Among chronic diseases, DM is that the foremost typical clarification for PN. Mechanisms involved in diabetes-associated PN unit of measurement mentioned full throughout a later section. Alternative endocrinological abnormalities which will result in pathology embody disorder and hypertrophy. The pathology related to adenosis usually manifests as carpal tunnel

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syndrome. Alternative manifestations like diabetic pathology, with tingling paraesthesia are during a stocking-glove distribution. PN of hypertrophy (excess growth hormone) includes carpal tunnel syndrome and activity polyneuropathy. Human immunological disorder virus (HIV) conjointly leads to PN, typically involving distal, nonpainful paraesthesias, shriveled articulatio talocruralis reflexes, and abnormal pain and temperature perception (3) illness is another chronic unwellness leading to PN. Peripheral pathology is common among chronic alcohol abusers, with prevalence as low as 9 % and as high as 50%. Alcohol-associated PN is expounded to a mixture of things, together with deficiency disease, nutrient deficiencies (thiamine in particular), and direct neurotoxicity of alcohol.

Pathogenesis of peripheral neuropathy

Demyelinating neuropathy

If the deceleration of nerve physical phenomenon affects all nerves roughly equally the designation is probably going to be the demyelinating sort of neuropathy (type 1). Seventy per cent of such patients have a duplication of the factor for a twenty-two kDa peripheral nerve myelin macromolecule on body seventeen (4). The duplication causes overexpression of the protein (4). The clinical picture ranges from classic claw foot with inverted champagne bottle legs to scarcely detectable clawing of the toes. Different mutations of constant macromolecule and of different myelin proteins cause an identical clinical image.

About 100% of patients with a demyelinating pathology have a body fluid paraprotein (4). Although often related to a solitary tumour, the paraprotein is usually benign. The commonest syndrome may be a slowly progressive preponderantly sensory pathology with AN IgMκ paraprotein. The paraprotein is AN antibody directed against the macromolecule epitopes on myelin associated compound protein. The antibody is directly responsible for the neuropathy.

Chronic inflammatory demyelinating polyradiculoneuropathy is that the most common quite no transmissible demyelinating pathology and affects regarding a try of per 100 000 of the population (5). The illness is typically preponderantly motor, and patients show a proximal as well as distal pattern of weakness; the condition may be relapsing and remitting. Protein concentrations within the body fluid square measure nearly always inflated (5). Chronic inflammatory demyelinating polyradiculoneuropathy is diagnosed by exclusion of the other causes from neurophysiological testing, which shows multifocal abnormalities with partial conduction block. This causes the compound muscle nerve impulse following proximal stimulation to be smaller than that following distal stimulation (5). It is thought to be a disease due to the inflammation within the nerves and response to therapy (6).

Chronic axonal neuropathy

Axonal polyneuropathy may be sensory or sensory and motor. It has several causes, which can usually be steered by the history or examination (7).

Such chronic idiopathic axonal neuropathy usually occurs in elderly people and is often indolent, predominantly sensory, and length dependent. Patients can be reassured that, although their condition may progress, it will usually do so only slowly and is unlikely to become seriously disabling.

Loss of pain and temperature sensation and spontaneous neuropathic pain, represented as burning or puncture, is distinguished symptoms of nerve fibre pathology. They are due to degeneration of thinly medullated and fat nerve fibres (7). Proof of the designation would need skin diagnostic test or enumeration of unmyelinated nerve fibres in lepton micrographs of a nerve diagnostic test specimen.

Chronic nerve fibre pathology happens in patients with several multisystem hereditary disorders. The identification of those conditions is typically steered by the opposite neurologic and general options (8). In this disease the symptoms usually begin in childhood and are associated with claw toes but may not come to attention until middle or old age. The condition is clinically and genetically heterogeneous, and a number of other cistron loci are concerned (8).

Alcohol-related neuropathy

Neuropathy related to chronic liver disease/alcoholism seems to be related to direct Ammendola et al found the strongest correlation was between incidence of nerve fibre pathology (most unremarkably of the sural nerve) and total period dose of fermentation alcohol, compared to alternative parameters examined (malnutrition and case history of alcoholism) (9). Alternative B-vitamin deficiencies, together with pteroylglutamic acid deficiency, have additionally been related to cases of alcohol-related pathology (10, 11).

Thyroid/Pituitary Neuropathies

Mucinous deposits in soft tissue leading to nervous disorder and carpal tunnel-like symptoms are involved in pathology related to gland disease (12). Neuropathy associated with excess growth hormone or acromegaly has been associated with sub perineurial-tissue proliferation and diminished myelinated and unmyelinated fibbers (12).

AIDS-associated neuropathy

Peripheral neuropathy affects as many as one-third of individuals with acquired immunodeficiency syndrome (AIDS), most commonly manifested as distal, symmetrical polyneuropathy. A study of 251 HIV-positive people found the incidence of pathology was considerably correlative with extent of immune deficiency (reflected in low CD4 counts) and deficiency disease (decreased weight, haemoglobin, and serum albumin) (13).

Drugs causing chemotherapy induced peripheral neuropathy

Chemotherapy Induced Peripheral Neuropathy (CIPN) is a side effect cancer patient and survivors are subjected to. This typically decreases the quality of life and manifests as paraesthesia, hyperalgesias, cold allondyia, myalgia, arthralgia disrupted motor activities and neurogenic pain. Enlisting the various chemotherapeutic agents and understanding their mechanism is key to establish an approach to manage the patients' resultant condition. CIPN is associated with many cancer chemotherapeutics but research has been done into a significant number of these.

The list includes Cisplatin, Oxaliplatin, Paclitaxel, Docetaxel, Epothilones, Bortezomib, Thalidomide, Lenalidomide, Pomalidomide, Vincristine and Suramin (14).

The various mechanisms by which these cause CIPN includes immune mediated mechanisms, alterations in the function of neuronal ion channels, degeneration of axons in myelinated neurons, altered calcium homeostasis within the cell and oxidative stress by the induction of reactive oxygen species (15).

Cisplatin and oxaliplatin

These two agents have been enlisted for the treatment of solid tumours and an important agent in the treatment of colorectal cancer as part of the FOLFOX regimen (16). By forming strong crosslinks between purine bases in the genetic material of the cell, Oxaliplatin disrupts the normal patterns of cell proliferation (16). Furthermore, inhibition of mRNA synthesis is achieved by the inhibition of RNA polymerases (17) ensuring a complete disruption of genetic activity and therefore cell death. Another mechanism of action is the initiation of an immune response via Interferon-gamma mediated T-Cell response (18). Cisplatin, is known for certain cytotoxic effects resulting from the disruption of mitochondrial functions to trigger oxidative toxicity – by which reactive oxygen species are released and these then damage nucleic and membranous materials of the cell – and the activation of the apoptotic pathways (19).

Cisplatin typically induces neuropathy by means of an axonal degeneration, intra-epidermal (nociceptor) loss, alteration of calcium homeostasis and mitochondrial dysfunction. Oxaliplatin shares an immune response mechanism by dissimilar underlying mechanisms to that of Cisplatin (Figure 1). Typically, Oxaliplatin mediates neuronal damage via inflammation while Cisplatin acts by altering the excitability of peripheral neurons.

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Paclitaxel and docetaxel

Belonging to the taxane group of agents, their usage appears dominant in the treatment of solid tumours.

Primarily they bind to microtubules comprising the cytoskeleton of the neuronal body, inducing damage to the axons and affecting signal transduction and retrograde and anterograde transport. Additionally, the neuronal inflammation pathway is triggered and alteration of the function of ion channels as well as alterations to the neuronal cell membrane (Figure 2).

Vincristine

Inclusive in MOPP, COPP and BEACOPP regimens for the treatment of Hodgkin's lymphomas, many paediatric neoplasms such as leukaemia's – it is hence used commonly. Vincristine interferes with cytoskeleton synthesis by binding to the beta-globin of microtubules (23).

Vincristine induces CIPN by means of an immune mediated response, resulting from cytokine release and the expression of integrins in the peripheral tissue. It affects microtubules as discussed, the myelin sheath, and alters calcium homeostasis of the cell resulting in changes in the membrane excitability factors (Figure 3).

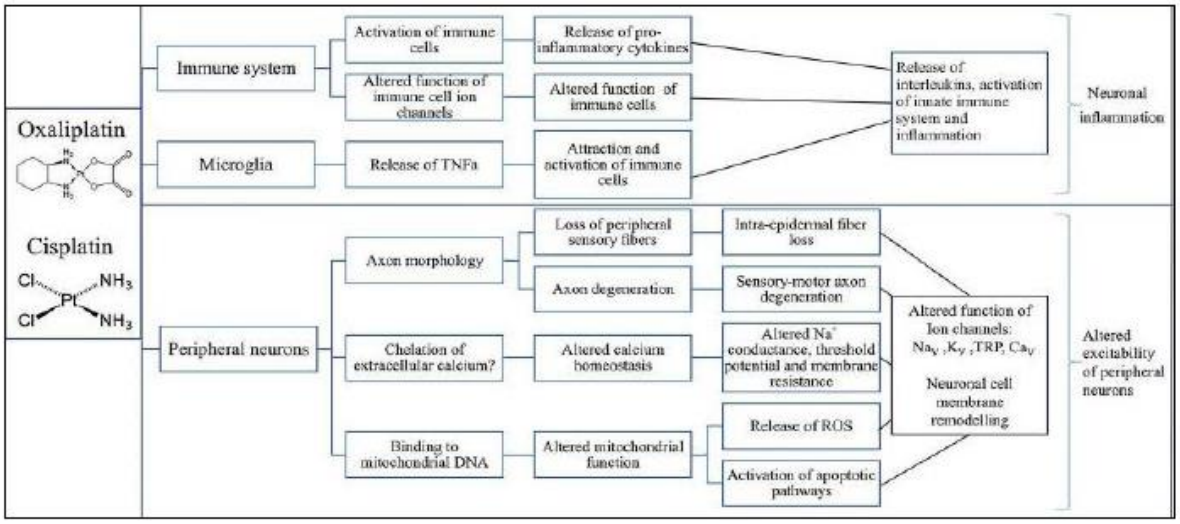

Figure 1. Adapted from: Starobova H., Vetter I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. Front. Mol. Neurosci. 2017 May 31; (10)

Illustrating the mechanisms of CIPN induced by chemotherapeutic agents Cisplatin and Oxaliplatin.

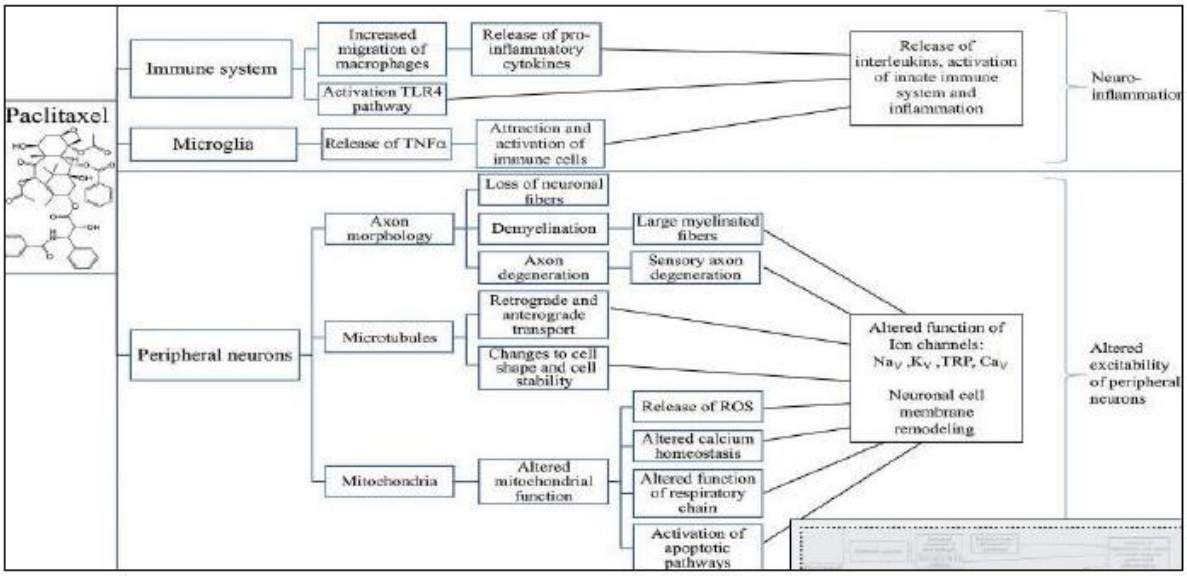

Figure 2. Adapted from: Starobova H., Vetter I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. Front. Mol. Neurosci. 2017 May 31; (10)

Illustrating the mechanisms of CIPN induced by chemotherapeutic agents Paclitaxel

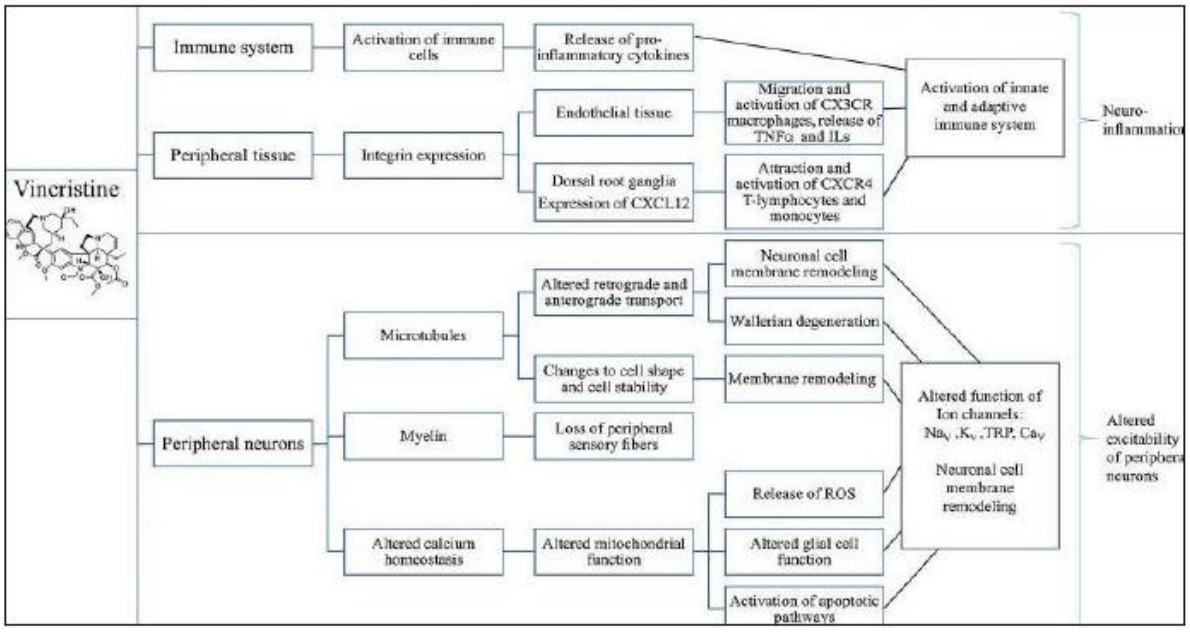

Figure 3. Adapted from: Starobova H., Vetter I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. Front. Mol. Neurosci. 2017 May 31; (10)

Illustrating the mechanisms of CIPN induced by chemotherapeutic agents Vincristine.

Bortezomib

Used typically for leukemoid cancers and it has been approved for usage in multiple myeloma, this agent works as a proteasome inhibitor (24).

Mechanisms inducing neuropathy are similar to previous agents such as mitochondrial altered homeostasis of calcium with the inclusion accumulation of Bortezomib in the Dorsal root Ganglion and dysregulation of neurotrophins (25). Table 1 summarizes the various mechanisms of neuropathy corresponding with the inducing drugs (26).

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Mechanisms of chemotherapy induced peripheral neuropathy

Table 1. Adapted from: Han Y. and Smith M. T. Pathobiology of cancer chemotherapy-induced peripheral neuropathy (CIPN). Front. Pharmacol. 2013 Dec 18.

Chemotherapy agent	Rodent CIPN models and human studies	Mechanism
Cisplatin Oxaliplatin	Male C57BL6 mice Female Wister Rats-cultured DRGs	Up-regulation TRPV1, TRPA1 and TRM8 TRPM8 and/or TRPA1 Over-expression; to cold allodynia
Cisplatin Oxaliplatin	Male SD rats	Activation of p38 MAPK and ERK1/2, along with downregulation of SAPK/JNK in cultured DRGs
Vincristine Paclitaxel	Male SD rats	Calcium increase either by influx extracellular Ca^{2+} or released from mitochondrial intracellular stores, binding to $\alpha_2\delta$ subunits of Ca^{2+} channel; decreased calcium
Paclitaxel	Human neuroblastoma cell line, SHSY-5Y	Activation of calpain, degradation of neuronal calcium sensor (NCS-1), and loss of intracellular calcium signaling
Paclitaxel Vincristine Cisplatin Oxaliplatin Bortezomib	Female/male Wister rats Male SD rats	NMDA receptor antagonist antagonize CIPN in prevention not intervention protocol or only at high dose
Oxaliplatin Cisplatin Vincristine	Male mice C57BL6J Male SD rats	DNA damage
Oxaliplatin	Male SD rats	Increase in PKC activity in supra-spinal regions
Paclitaxel but Not Oxaliplatin	Male SD rats – cultured DRGs	Increased released of substance P and altered CGRP and somatostatin release
Cisplatin Paclitaxel	Female patients Female Wistar rats	Decreased in NGF levels by Total Neuropathy Score (TNS) in patients and in rat plasma samples
Oxaliplatin	Patients Rates	Dysfunction of axonal Na^+ channels Dysfunction of axonal K^+ channels

Enlisting the numerous drugs and their brief mechanisms of inducing CIPN.

Immune mediated injury

Mechanical hyperalgesia and the loss of intra epidermal fibres due to oxaliplatin and paclitaxel has been shown to be mediated by monocytes and microglia, indicated by decreased neuropathy after administering antibiotics known to inhibit these cells (26, 27).

Agents triggering an increase in levels of specific cytokines (IL-6, il-1 beta, TNF-alpha) have also been shown to sensitize nociceptors leading to neuralgic presentations (28).

Increased expression of integrins on the surface of endothelial expressions gives way for macrophage (CXCR3) migration into nervous tissue, allowing macrophage induced injury (29). This can also be mediated by increased chemokine leukin-12 in dorsal horn ganglia which attracts T-Lymphocytes and monocytes leading to activation of these which increases intracellular Ca^{2++} and illicit attraction of immune cells to the inflamed site. This is caused by the increased binding affinity of STAT3 to the CXCL 12 genepromoter (28).

Altered calcium homeostasis

Certain drug metabolites, such as oxalate from oxaliplatin, acts as Ca^{2+} chelators. The chelation favours an influx of Na^{+} initiating an action potential (31). Mitochondrial depolarization triggered by chemotherapeutic agents that activate a Mitochondrial Permeability Transition Pore initiate depolarization of the mitochondria and the release of Ca^{2+} (32).

Apoptosis and stress by oxidative species

Chemotherapeutic agents targeting mitochondrial DNA, lead to an alteration of function or disruption of the membranous integrity of the organelle which can trigger a dysfunction. Results are a generation of reactive species, typically oxygen species (33). These species are known to destroy proteinaceous and lipid-based components in the cell, resulting in damage to organelle and cell membranes including genetic material damage. The presence of these molecules also triggers the Cytochrome C and Bax initiation of apoptosis (33) leading to neuronal damage. An inclusive finding leading to mitochondrial dysfunction is that of increased vacuolation and mitochondrial swelling (34).

Altered neuronal excitability

Changes to the ion channel function and expression induce changes in action potentials favouring the propagation of such. Increased expression of Na channels at the Nodes of Ranvier along axons (35) and alterations in their function (36) have been shown with usage of agents such as Oxaliplatin. A decreased expression of K+ channels was also found in subjects with Oxaliplatin exposure (36).

Methods

Background searches into peripheral neuropathy and the chemotherapeutic agents that induce CIPN and their mechanisms was done from a series of journal databases including PubMed, SCOPUS, Frontiers, Science Direct and Nature's series of Journals.

Treatment options were sought from the same databases dating between 2003 and 2019. From this the therapeutic options that have been explored and tried and the updates to these have been enumerated as discussed.

Discussion

Chemotherapy-induced peripheral neuropathy cannot be regarded as a homogeneous syndrome, given the great variety of cytostatic drugs exhibiting different modes of damaging the PNS (37). The treatment options available for the management of CIPN are almost as diverse as the etiologies, due to the diversities of the underlying initiating events, patient populations and manifestations of the different types of pain, hence there is no way to determine a particular therapy and the response of an individual to that particular therapeutic intervention (38).

The treatment of CIPN remains largely ineffective. Although different strategies have been attempted, no pharmacological agent has yet been shown to be helpful. As a result, many patients are forced to reduce the dosage or discontinue potentially curative neurotoxic drugs, on a trial and error basis [38].

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Hence there is no best or ideal treatment option. However, over the years several therapeutic strategies have been postulated, even though much research and clinical trials are still needed before the usage can be approved. Nevertheless, evidence has established a set of first-line drugs for usage in the management of CIPN. Among other researches, complementary therapeutic approaches include the use of combination therapy in polypharmacy, preventative medicines, medicinal plants and psychological management.

CIPU patients should be treated on a holistic level that considers all aspects of patient well-being. Pain, depression, and anxiety are highly interrelated, greatly impairing quality of life in those with cancer [39]. In Box 1 the various therapeutic options available for patients suffering from CIPU are highlighted. Recently, most treatment options have a higher affinity towards non-pharmacological therapies such as medicinal herbs.

The goal of most treatments is to limit the intense pain experienced by patients from their specific chemotherapy agents causing severe neuropathic pain over a course of time.

Box 1. Key points: Treatment of CIPU
Pharmacological treatment Preventative therapy Polypharmacy combinations First-line therapy Non-pharmacological treatment Medicinal plants Complementary therapies Psychological treatment Rehabilitation, Physical Therapy and Safety Factors

Pharmacological therapy

Preventative drugs

The application of preventative drugs will not exert a significant impact on the progression of the neoplastic disease. Preventative treatments are aimed at trying to reduce the incidence or severity of CIPN in patients actively receiving neurotoxic treatments (40).

In 2003, Paice mentions that clinical studies were underway to evaluate the use of glutamine and glutathione to prevent CIPN. By 2009, Kaley and DeAngelis stated that in order for these preventative drugs to be beneficial it must reduce the neurotoxic effect of the drugs while not interfering with its anti-tumour property. They provided evidence for the uses of these preventative drugs by the results from clinical trials conducted. This concept was further developed in 2012, in which the efficacy of these drugs was revised by Brzezinski. Evaluation of these drugs was based on their effectiveness as a preventative drug and its impact of the chemotherapeutic activity. These drugs include calcium and magnesium ions, vitamin E, glutathione, glutamine, *N*-acetylcysteine, acetyl-L-carnitine, human recombinant interleukin and antiepileptic drugs. The cumulative results from this study are seen in figure 4.

Tested drug	Cytostatic drug	Limitations	Conclusions	
			PREV (+/–)	CHEM (+/–)
Ca^{2+}, Mg^{2+} ions	oxaliplatin		+	
vit. E 600 mg	cisplatin		+	+
amifostine	cisplatin, paclitaxel		+/–	+/–
glutathione	cisplatin	(small group)	+	+
glutamine	paclitaxel		+	?
N-acetylcysteine	oxaliplatin		+	?
acetyl-L-carnitine	cisplatin, paclitaxel	(no placebo, small group)	+	?
carbamazepine	oxaliplatin		–	?
oxcarbazepine	oxaliplatin	(no placebo, small group)	+	?
venlafaxine	oxaliplatin	(no placebo, small group)	+	?

PREV – effectiveness of prevention, CHEM – impact of the drug on chemotherapeutic activity, (+) – positive, (–) – negative

Figure 4: List of drugs tested for their effectiveness in CIPN prevention. Adapted from Brzezinski (2012), Chemotherapy-induced peripheral neuropathy. Part II. Prevention

Published in 2014, the ASCO guidelines on the prevention of CIPN, based on a systematic review of 42 randomized controlled trials investigating 18 agents, found that there are no agents that have shown consistent, clinically meaningful benefits for CIPN prevention (41). These guidelines have several recommendations against and for the use of certain drugs used in both treatment and prevention, of which are found in table 2.

Table 2. ASCO guidelines for treatment and prevention of CIPN. Adapted from Stenger (2014) ASCO Releases Guidelines on Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers

Agent	Recommendations
Prevention Recommendations	
Acetyl –L- carnitine	Strong against, with high strength of evidence, no evidence of efficacy and high evidence of harm
Amifostine	Moderate against, with intermediate strength of evidence, low evidence of efficacy and moderate evidence of harm
Amitriptyline	Moderate against, with intermediate strength of evidence, no evidence of efficacy and moderate evidence of harm
Calcium and Magnesium for patients receiving oxaliplatin-base chemotherapy	Moderate against, with high strength of evidence and low evidence of efficacy and harm
Diethyldithio-carbamate	Strong against, with low strength of evidence, no evidence of efficacy and high evidence of harm
Glutathione for patients receiving paclitaxel/carboplatin chemotherapy	Moderate against, with intermediate strength of evidence and low evidence of efficacy and harm
Nimodipine	Strong against, with low strength of evidence, no evidence of efficacy and moderate evidence of harm

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Org 2766	Moderate against, with intermediate strength of evidence and low evidence of efficacy and harm
Retinoic acid	Moderate against, with low strength of evidence, low evidence of efficacy and moderate evidence of harm
rhuLIF or emfilermin	Moderate against, with low strength of evidence, no evidence of efficacy and low evidence of harm
Vitamin E	Moderate against, with intermediate strength of evidence and low evidence of efficacy and harm
Venlafaxine	Insufficient information for recommendation, with intermediate strength of evidence and moderate evidence of efficacy and harm
Acetylcysteine, carbamazepine/oxycarbazepine, glutamate or glutathione for patients receiving cisplatin or oxaliplatin-based chemotherapy, goshajinkigan or omega-3 fatty acids.	Inconclusive recommendation, with low strength of evidence and low evidence of efficacy and harm for all
Treatment Recommendations	
Acetyl-L-carnitine	Low strength of evidence, low evidence of efficacy, moderate evidence of harm.
Tricyclic antidepressants (nortriptyline/amitriptyline)	Intermediate strength of evidence, low evidence of efficacy and harm.
Gabapentin	Intermediate strength of evidence, low evidence of efficacy and harm
Topical gel treatment containing baclofen (10mg) amitriptyline (40mg) and ketamine (20mg)	Intermediate strength of evidence, moderate evidence of efficacy and low evidence of harm

Polypharmacy combinations

CIPN treatments are usually adjusted based on the desired effect that will be of maximal benefit to the patient. Basis for treating CIPN patients is to administer one drug at a particular time period, then the drug is gradually titrated to a higher dose as long as the harm does not outweigh the benefit of the drug or simply it is switched with a similar or different drug.

In 2005, the concept of drug combinations was proposed to treat CIPN by Gilron and Max. They postulated that having a combination of drug acting via different mechanism can further improve pain relief with less side effects.

Benefits of combining an opioid with a non-opioid adjuvant include enhanced analgesic efficacy, broader analgesic spectrum, decreased opioid dose and prevent opioid tolerance. In chronic pain management, drug interactions are of concern. Therefore, close observation is required with certain drug combinations.

First-line therapy

In 2003, Paice introduces an algorithm for management of neuropathic pain, shown in figure 5. The algorithm commences with an evaluation of the patient to establish a baseline upon which to gauge the efficacy of the therapy. Drugs considered as first-line therapy includes anticonvulsants, corticosteroids, local anaesthetics, opioids and tricyclic antidepressants. By 2009, these categories of drugs were still given as first line for symptomatic treatment and were under further investigations.

Most of these drugs are not standardized and their usage is dependent on patient tolerability and the diverse pathogenesis involved in CIPN.

In 2015, Kajih and Moore proposed a list of drugs for pharmacological treatment given in table 3, with Duloxetine being the only pharmacologic therapy recommended in the American Society of Clinical Oncology (ASCO) clinical practice guidelines for treatment of CIPN in patients with cancer (42). While the other drugs have been under investigation for their efficacy in treating CIPN. Further in 2015, Trivedi et al, through randomized controlled trials for the treatment of CIPN, showed that antiepileptic, antidepressants and topical drugs were of limited success (41). Results of these trials are shown in table 4.

CIPN does not have a standardized treatment protocol due mainly to the fact that it manifests itself in several diverse pathogeneses and etiologies. Thereby, making each treatment specific to the patient and the underlying cause.

Considering this fact, in 2014 Cohen and Mao summarizes several mechanisms involved in the development of CIPN and its specific treatment, seen in figure 6.

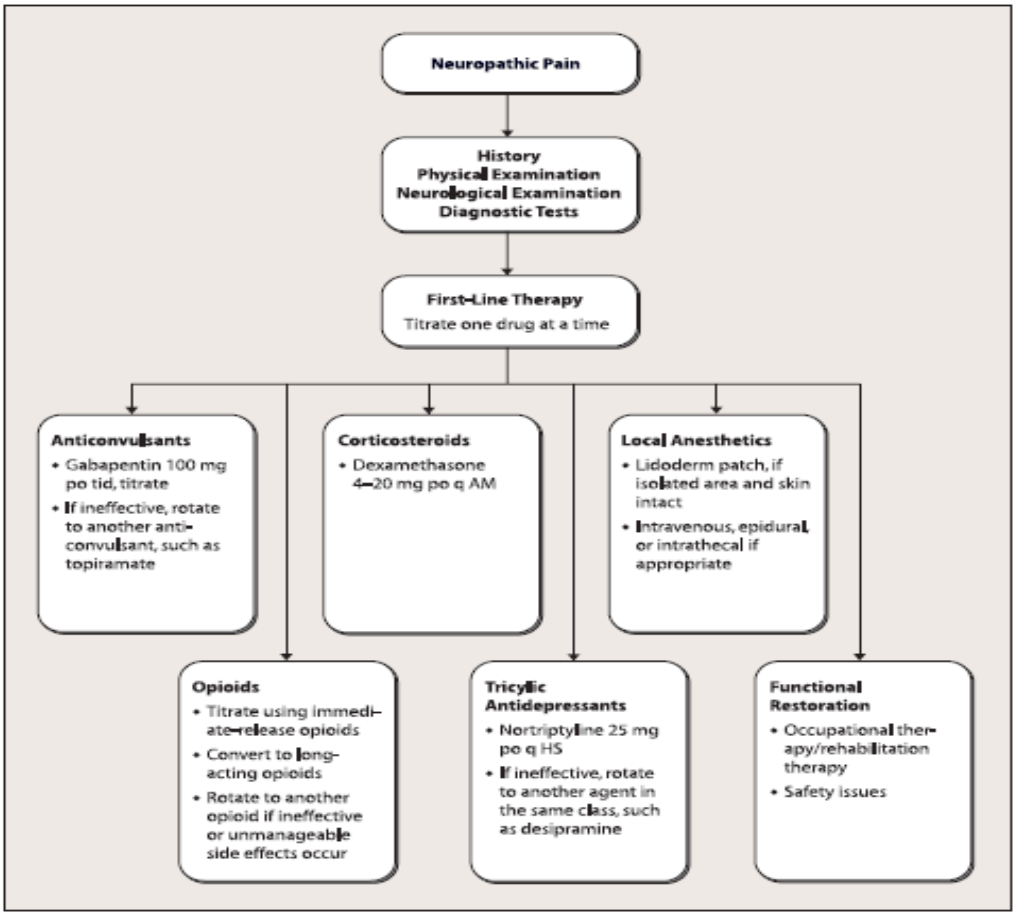

Figure 5. Algorithm for Management of Neuropathic Pain. *Adapted from Paice (2003) Mechanisms and Management of Neuropathic Pain in Cancer*

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Table 3. Pharmacological treatment strategies for CIPN. Adapted from Kajih and Moore (2015) Management of Chemotherapy-Induced Peripheral Neuropathy

Drugs	Dosage
Duloxetine	30 mg/day for 1 wk, increase to 60 mg/day
Tricyclic antidepressants	Amitriptyline: 25-100 mg/day; max dose 200 mg/day Nortriptyline: 10-25 mg/day initially; titrate to effective dose (usually 75 mg/day)
Anticonvulsants	Gabapentin: 300-900 mg/day; titrate to 3,600 mg/day Pregabalin: 150 mg/day initially; may titrate up to 600 mg/day (max dose)
Topical products	Compounded gel containing baclofen 10 mg, amitriptyline 40 mg, and ketamine 20 mg applied bid
NSAIDs	Ibuprofen 600 mg qid
Opioids	Tramadol slow-release tablets: 200-400 mg/day Oxycodone CR: 10 mg tablet q12h; may titrate every 3 days to a max dose of 60 mg q12h

CIPN: chemotherapy-induced peripheral neuropathy; CR: controlled release; max: maximum; NSAID: nonsteroidal anti-inflammatory drug.
Source: References 2, 8, 15-17.

Table 4. Phase 3 Randomized, Placebo-Controlled CIPN Treatment Trials. Adapted from Trivedi (2015) Management of Chemotherapy-Induced Peripheral Neuropathy

Pharmacologic agent and dosage	**Drugs causing CIPN**	**Primary study outcome measure and results**	**Overall Result**	**Adverse effect of interaction**
Amitriptyline 10mg daily with dose escalation of 10 mg/week up to target maximum dosage of 50 mg daily for 8 weeks	Vinca alkaloids, platinum agents, or taxanes	Global improvement as assessed by numeric scales (scales, 0-100) in dairy data c no significant difference in mean score between group (3.4±3.6 vs 1.9±3.1in placebo arm; P=NS). Global improvement at final visit assessed by verbal rating scale (scale, complete relief-symptoms worse); no significant difference between group (47% vs 31% in placebo arm; P= NS),	Negative	Tiredness Tachycardia
Nortriptyline(N) 25 mg daily with dose escalation of 25 mg/week up to target maximum dosage of 100 mg during treatment period	Cisplatin	Paraesthesia as assessed by visual analog scale: in first treatment period, no significant reduction in paraesthesia (49 vs 55{scale,0-100} in placebo arm; P=.78).	Negative	Dry mouth Dizziness Constipation
Venlafaxine 50 mg 1h prior to oxaliplatin infusion and 37.5 mg extended- release twice daily on days 2 through 11	Oxaliplatin	Full relief of acute neurotoxicity: 31.3% vs 5.3% in placebo arm (P=.03)	Positive	Grade 1-2: Nausea and Vomiting Asthenia, Somnolence
Duloxetine (D) 30 mg	Paclitaxel,	Reduction in average pain	positive	Fatigue (7%)

daily for 1 week, then 60 mg daily for 4 weeks during	dicetaxel, nanoparticle albumin-bound paclitaxel, cisplatin, oxaliplatin	as measured by BPI-SF: in initial treatment period, larger mean reduction in BPI-SF pain score in duloxetine group than placebo group (1.06 vs 0.34{scale,0-10}; P=.003) with moderately large effect size (0.513).			Insomnia (5%) Nausea (5%)

Antiepileptic	Gabapentin(G) 300 mg with dose escalation of 300 mg to a target maximum dosage of 2700 mg daily for 6 weeks during treatment period	Vinca alkaloids, Taxanes, or platinum agents	Averages pain by NRS and ENS: no difference in NRS or ENS score at baseline 6weeks or 4 weeks between groups	Negative	No significant difference in toxicities between group
	Lamotrigine 25 mg at bedtime for 2 weeks, then 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks, then 100 mg twice daily for 2 weeks, then 150 mg twice daily for 2 weeks	Vinca alkaloids, Taxanes, or platinum agents	Averages pain by NRS and ENS: no difference in NRS or ENS score at baseline or 10 weeks between groups	Negative	No significant difference in toxicities between group
Topical	Baclofen, amitriptyline, and ketamine gel, 1.31 g of compounded gel containing 10 mg baclofen, 40 mg am	Vinca alkaloids, Taxanes, or platinum agents	EORTC CPIN sensory subscale mean neuropathy change from baseline to 4 weeks: 8.1 vs 3.8 in placebo arm(P=.053)	Negative	No significant difference in toxicities between group
	Arnitrptyline and ketamine (AK) cream 4 g twice daily for 6 weeks	Taxanes or notaxanes	Mean pain, numbness, and tingling score at week 6: no significant	Negative	No significant difference in toxicities between group

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			reduction in mean score (P= 363		

Non-pharmacological therapy

Medical plants

CIPN patients already succumb to numerous amounts of medications per day. A different perspective is to reduce on the quantity of chemical consumed by these patients, which can build up and eventually cause toxicity. Considering that these medical plants does not interact with the chemotherapeutic agents to decrease their efficacy. It is more beneficial to the patient than pharmacological treatments, which can be a substantial burden to the patient as well as increase healthcare costs. Medicinal plants are the most recent approach to managing CIPN in 2019, proposed by authors Wu et al. Majority of these plant extracts are used because their active compound has natural anti-inflammatory and antioxidant properties which can help counteract the inflammatory effects of chemotherapeutic drugs on peripheral nerves.

Complementary therapies

There are several different avenues patients take for relief of their neuropathic pain when they their prescription medications are no longer effective. They are considered complementary since they can be used simultaneously with chemotherapeutic drugs and have little to no interaction with these drugs. Such therapies include the use of acupuncture, among others which have readily decreased pain experienced by these patients. Table 5, displays a list of complementary therapies that can be used for treatment of CIPN.

Psychological therapy

Painful neuropathies can significantly impair the quality of daily life of those suffering from cancer, especially correlating with the depression and anxiety. Several studies have shown that pain can directly affect mood and daily activities such as work, sleep and socializing.

Cognitive behaviour techniques can be employed as adjuvants to pharmacological therapies and can help patient develop positive coping methods in dealing with difficult situations such as extreme pain. Examples of these techniques include hypnosis, meditation and imagery.

Rehabilitation, physical therapy and safety factors

An essential consideration is managing chronic neuropathic pain from CIPN. This provides a safe environment for these patients which can help them avoid serious accidents such as sudden fatal falls, especially in patients with lower functional dependence in performing simple tasks such as getting dressed.

Physical therapy can improve functional muscle strength, which can improve coordination and sensory integration. Expressive arts and relaxation prayers. These can further help to improve mood and provide a sense of control to the patient.

Ankle foot orthotics (AFO)–type braces, which fit easily within a standard shoe, can help prevent falls when patients experience a slapping gait or foot drop (39).

Practical safety measures include advising patients who are insensitive to heat to test the temperature of water in their home to avoid scalding, wear gloves while washing dishes and to use pot holders when cooking. Walkways in the home should be clear, with no throw rugs that could lead to falls. Well-lit hallways and the use of nightlights may prevent falls. Non-skid shower and tub mats will also help prevent falls while bathing (39).

Future scope of studies

Despite the existence of CIPN over the past decade, not much significance has been given to its treatment. As majority of treatment options available are directly linked to the underlying

chemotherapeutic agent being used. It is clear that this is an area that requires much future researches to help CIPN patients. Box 2 demonstrates a list of future research questions.

Box 2: Key Research Questions
Clinical trials should be conducted among patients using both medical herbs and preventative drugs to test their combined efficacy A comparison between medicinal plants and first line drugs. Pain relief among patients using complementary therapies and those using pharmaceutical drugs.

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