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Review

Mechanisms and therapeutic perspectives of chemotherapy-induced peripheral neuropathy: an update

Antonio Avallone[1], Sabrina Bimonte[2]*, Claudia Cardone[1], Cira Antonietta Forte[2], Marco Cascella[2] and Arturo Cuomo[2]

[1] Abdominal Oncology Division, Naples, Italy. a.avallone@istitutotumori.na.it; claudia.cardone@istitutotumori.na.it.
[2] Division of Anesthesia and Pain medicine Istituto Nazionale Tumori IRCCS Fondazione Pascale - IRCCS di Napoli; s.bimonte@istitutotumori.na.it, c.forte@istitutotumori.na.it; m.cascella@istitutotumori.na.it; a.cuomo@istitutotumori.na.it,
*Correspondence: s.bimonte@istitutotumori.na.it; Tel.: +390815903221, S. B.

Simple Summary: Chemotherapy-induced peripheral neuropathy (CIPN) is a peripheral neuropathy emerging after a chemotherapy treatment. The most common clinical manifestation of CIPN is sensory axonal neuropathy with motor and autonomic involvement. Persistent CIPN symptoms are associated with an increased risk of falling, disability, and psychosocial distress, thus affecting dramatically the patient's quality of life (QoL). This disease has complicated pathophysiology featured by underlying mechanisms not completely known. Although many pharmacological and non-pharmacological therapeutic approaches have been tested to overcome these symptoms, there is currently no standardized cure to prevent or treat CIPN.

Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) develops as a challenging nerve-damaging adverse effect of anticancer drugs used in chemotherapy. The disorder may require a dose reduction of chemotherapy and its most common sensory symptoms are severe pain, tingling, and numbness in the hands and feet. CIPN affects dramatically the patient's quality of life (QoL). Pain and sensory abnormalities may occur for months, or even years after the termination of chemotherapy. This disease has complicated pathophysiology featured by underlying mechanisms not completely known. Although many pharmacological and non-pharmacological therapeutic approaches have been tested to overcome these symptoms, there is currently no standardized cure to prevent or treat CIPN. According to current guidelines, Duloxetine is the only recommended agent for painful neuropathic symptoms. Therefore, finding effective therapies for CIPN is mandatory. The purpose of this review is to dissect CIPN, the target and immunotherapy-based approaches to this disorder, as well as to offer new insights for novel therapeutic perspectives.

Keywords: Chemotherapy-induced peripheral neuropathy, pain management, target therapy, immunotherapy

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1. Introduction

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a common side effect of cancer therapy, affecting approximately 40% of patients receiving active treatment. The pathophysiology of CIPN is very complex and is due to a series of processes according to the type of chemotherapy used, although the underlying molecular mechanisms are still unknown [1-4]. Many agents are associated with peripheral neurotoxicity including chemotherapy, such as platinum derivates, taxanes, vinca alkaloids, proteasome inhibitors, Bortezomib, immunomodulatory agents and several classes of biological agents such as targeted therapies, multikinase inhibitors, immunotherapy, and antibody-drug conjugates [5, 6]. The most common clinical manifestation of CIPN is sensory axonal neuropathy with motor and autonomic involvement. Persistent CIPN symptoms are associated with an increased risk of falling, disability, and psychosocial distress [7]. Moreover, as symptoms have been reported to be dose-dependent on the chemotherapy used, prolonged treatment may reduce the survival rate of patients [8,9]. No biomarker has demonstrated clinical validity for diagnosing and monitoring CIPN, although serum determination of neurofilament light (NfL) appears to be a promising tool [10]. Currently, the main approach to prevention and treatment of iatrogenic peripheral neurotoxicity relies on dose modifications and the adaptation of schedules with a shorter treatment duration or premature cessation of the neurotoxic drug in case of severe symptoms. To date, despite several randomized trials conducted, no agent has been recommended for the prevention of CIPN. Many preventative interventions have been proposed including exercise, acupuncture, cryotherapy, and ganglioside monosialic acid. However, their use has no clinical indication [11, 12]. Furthermore, preventative strategies may have unanticipated consequences. The use of preventive acetyl-L-carnitine in patients treated with taxanes was associated with a paradoxal CIPN worsening. In a recent long-term follow-up analysis of a large double-blind randomized trial, 24 weeks of acetyl-L-carnitine therapy resulted in significantly worse CIPN, as measured by the Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-Ntx) Questionnaire [13]. Therapeutic options for patients with CIPN are very limited. Topical local interventions such as the use of 1% menthol cream, Topical baclofen, amitriptyline, ketamine, and Capsaicin 8%-containing patches, in absence of safety concerns, have been introduced in clinical practice based on limited data available [14-16]. According to current guidelines, Duloxetine is the only recommended agent for painful neuropathic symptoms. A large randomized trial demonstrated a moderate clinical benefit in patients with painful CIPN treated with duloxetine versus placebo, with a higher rate of pain reduction (59% versus 38%) [17]. Alternatively, a small randomized trial supports the use of Venlafaxine [18]. In addition, membrane-stabilizing agents such as pregabalin, amitriptyline, and opioids, should be used as salvage therapy [19-20]. Non-pharmacological approaches such as scrambler therapy, acupuncture, and exercise may reduce established CIPN symptoms and appear to be reasonably safe [21]. Limited data are available, and more research is needed to determine the clinical utility of these approaches in the treatment of CIPN. The ceramide-to-S1P rheostat is emerging as a critical regulator of the pain pathway. The functional significance of genetic variations within the ceramide-to-S1P rheostat is an object of further investigation to gain a better understanding of neuropathic pain pathogenesis. In this context, FTY720 (fingolimod, Gilenya®), an S1P receptor modulator, the first FDA-approved medicine as an orally bioavailable drug for treating relapsing forms of multiple sclerosis, has raised hopes for treating neuropathic pain disorders. Fingolimod, is currently being investigated in several trials for the management of CIPN [22]. Future trials should adopt a multimodal methodological approach, with the implementation of subjective (patient-reported) outcomes as primary endpoints and objective (neurophysiological; imaging) outcomes as secondary endpoints, to reveal the full extent of CIPN abnormalities, their impact on patient's function, and quality of life and to dive insights into the pathophysiology of symptomatic CIPN. Therefore, finding effective therapies for CIPN is mandatory. The purpose of this review is to dissect CIPN, the target and immunotherapy-based approaches to this disorder, as well as to offer new insights for novel therapeutic perspectives.

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2. Mechanisms of chemotherapy-induced peripheral neuropathy

Multifactorial mechanisms induced by chemotherapy-based cancer therapy are causative of CIPN and involve mitochondrial damage and oxidative stress, microtubule disruption, impaired ion channel activity, myelin sheath damage, DNA damage, neuroinflammation, and immunological processes [23] (**Table 1**).

Table 1. The mechanisms of CIPN induced by chemotherapeutic agents

Chemotherapeutic agent	Mechanism of CIPN	Pathways	References
Platinum-based chemotherapeutic drugs (oxaliplatin, cisplatin and carboplatin)	Neuroinflammation (activation of microglia, astrocytes); Altered excitability of peripheral neurons (mitochondrial damage, altered activities of ion channels	ROS, oxidative stress, Interleukin and Chemokines, CX3CL1 and CXCL12, TNF-α, MAPK chinase, caspases.	[21-46]
Immunomodulatory drugs (thalidomide)	Altered excitability of peripheral neurons (antiangiogenic effect, acceleration of neuronal cell death, apoptotic changes of peripheral nerves)	TNF-α , NF-kB	[47-49]
Vinca alkaloids (vinblastine, vinorelbine, vincristine, vindesine)	Neuroinflammation (Nociceptors sensitization); Hyperexcitability of peripheral neurons (inhibition of polymerizations into microtubules, Wallerian degeneration, and an alteration of activity of ion channels)	Interleukins	[50-53]
	The disruption of microtubules causes Wallerian degeneration, altered activity of ion channels, and altered excitability of peripheral neurons.	ROS	[54-57]

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Taxanes (paclitaxel, docetaxel and cabazitaxel)	Neuroinflammation (activation of microglia and astrocytes, nociceptor sensitization, damage of mitochondrial DNA transcription); Alteration of excitability of peripheral neurons (microtubule disruption; alteration of functions of ion channels)		[58-60]
Protease Inhibitors (Bortezomib)	Alteration of excitability of peripheral neurons (impairment of sphingolipid metabolism in astrocytes, mitochondria damage)	ROS, interleukin 1-β and TNF-α.	
	Neuroinflammation (activation of monocytes and T-lymphocyte);		
Epothilones	Alteration of excitability of peripheral neurons (impairment of sphingolipid metabolism in astrocytes, mitochondria damage);	ROS	[61]
	Neuroinflammation (activation of monocytes and T-lymphocyte)		

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Accumulated pre-clinical and clinical studies, demonstrated that platinum-based chemotherapeutic drugs, induce CIPN or by neuroinflammation resulting from glia cell activation, or by alteration of excitability of trigeminal ganglion (TG) and dorsal root ganglion (DRG) neurons, due to the change of ion channels voltage [24-26]. Moreover, cisplatin, commonly used for the treatment of various types of cancer, can induce peripheral neuropathy in a dose-dependent manner [27-28]. The neurotoxic effect induced by platinum-based chemotherapeutic agents is strictly associated with their different anticancer mechanisms (affecting mainly mitochondria) which impair the functions and the structure of glial and neuronal cells [29-30]. Different studies demonstrated that platinum drugs induce an impairment of mitochondria function, and an increased level of ROS (reactive oxygen species), thus resulting in oxidative stress. This complex cascade of events leads to the degeneration of DRG neurons causing neuropathy [31-35]. Moreover, oxaliplatin (mainly used for the treatment of gastrointestinal tumors) and cisplatin produce an alteration of intracellular calcium signaling pathways (MAPK chinase and caspases), thus leading to DRG neuron apoptosis [36-37]. Animal studies demonstrated that oxaliplatin induces peripheral neuropathy by altering the potential action of different ion channels: transient receptor potential (TRP) channels, sodium channels (NaV), and potassium channels (KV) [36-41]. Interestingly, different studies demonstrated that oxaliplatin, by activating the pro-inflammatory cytokines tumor necrosis factor-alfa (TNF-a), interleukin-beta (IL-1b), and IL-6 and the related receptors, interferes with the activity of the neurotransmitter GABA (gamma-aminobutyric acid) and induces allodynia [42]. Similarly, studies showed that oxaliplatin increased the level of chemokines, C-X3-C Motif Chemokine Ligand 1 (CX3CL1), and C-X3-C Motif Chemokine Ligand 12(CXCL12), and their ligands, Chemokine ligands (CCLs), thus enhancing the peripheral neuropathy [43-46]. Several evidences highlighted that the immunomodulatory drugs, particularly, thalidomide, induced CIPN, by altering the excitability of peripheral neurons through the inhibition of nuclear factor kappaB (NF-kB) and the deregulation of TNF-α pathways, leading to increased cell death [47-50]. Similarly, to platinum drugs, vinca alkaloids (vinblastine, vinorelbine, vincristine, vindesine), used in the treatment of different types of lymphoma, cause CIPN through two different processes. The first is the neuroinflammation caused by an increased release of pro-inflammatory cytokines (interleukins and chemokines); the second is the hyper excitability of peripheral neurons induced by the inhibition of polymerizations into microtubules, Wallerian degeneration, and an alteration of the activity of ion channels [51-53]. Taxanes (i.e. paclitaxel, docetaxel, and cabazitaxel) mainly used for the treatment of breast, ovarian, and prostate tumors, induce CIPN through a complex mechanism involving, the disruption of microtubules leading to Wallerian degeneration, the altered activity of ion channels and the altered excitability of peripheral neurons. Neuroinflammation results because of nociceptor sensitization due to damage of mitochondrial DNA transcription, a releasing of reactive oxygen species (ROS), and demyelination of peripheral neurons. [54-57]. Again, protease inhibitors, particularly bortezomib used for the management of lymphoma and myeloma, can induce CIPN by a complex process involving different mechanisms. Specifically, bortezomib provokes an upregulation of interleukin-1β (IL-1β) and TNF- α, which in turn causes impairment of sphingolipid metabolism in astrocytes, and an alteration of excitability of peripheral neurons [59-60]. Similarly, bortezomib by damaging the mitochondria, increases ROS production and provokes an apoptotic change at the level of peripheral neurons. Contemporarily, by activating the monocytes and T-lymphocyte and by increasing the ROS production, bortezumib releases pro-inflammatory cytokines, leading to neuroinflammation [61]. Finally, epothilones, mainly used in the treatment of breast cancer, induce CIPN with mechanisms like those described for bortezomib [62-63]. More studies are necessary, to shed a light on the different mechanisms underlying CIPN and to set up appropriate schedules of prevention and treatments.

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3. Treatments and assessments of chemotherapy-induced peripheral neuropathy

Many pharmacological and non-pharmacological therapeutic approaches have been-tested for the efficacy in CIPN treatment (**Figure 1**).

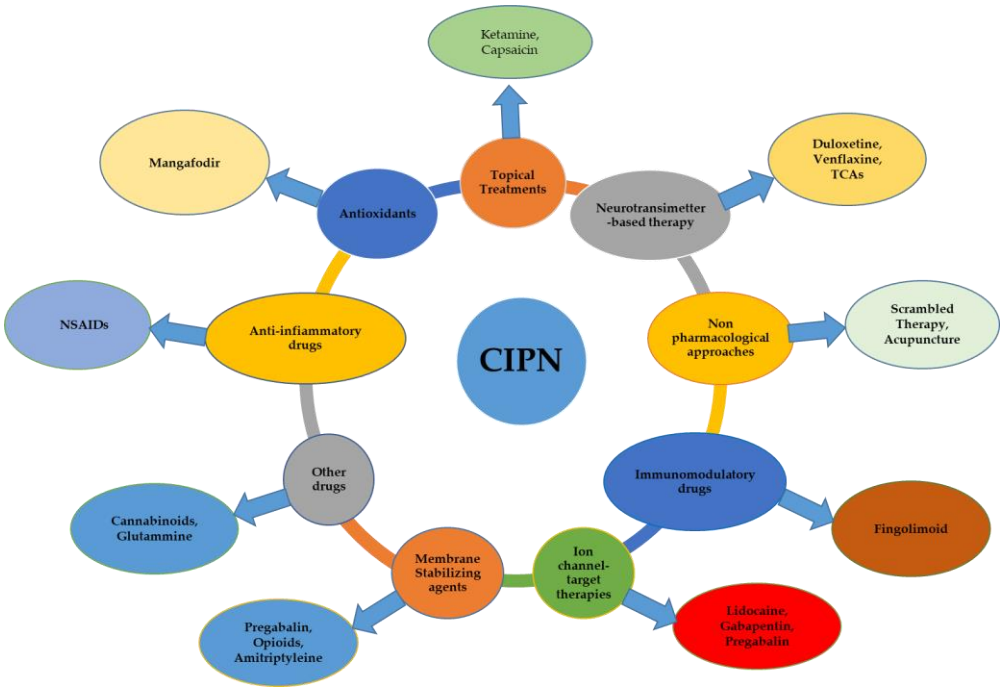

Figure 1. Treatments of CIPN. The cartoon recapitulates the pharmacological and non-pharmacological therapeutic approaches tested for the efficacy in CIPN treatment.

Topical intervention as baclofen, amitriptyline, ketamine, and Capsaicin 8%-containing patches, in absence of safety concerns, has been introduced in clinical practice based on limited data available [14-16]. Particularly, studies performed with Capsaicin 8%-containing patches, highlighted a good efficacy in treating CIPN without unsupportable side effects [64-65]. Accumulated pieces of evidence highlighted the potential therapeutic effects on CPIN of ion channels-target therapy. Promising results were obtained from the studies conducted with the anticonvulsant medications, gabapentin and pregabalin, while infusion with calcium magnesium or sodium gave discouraging data. Both pregabalin and gabapentin are able to bind to the alpha2-delta protein and thus altering the potential of action of the ion calcium channel, although pregabalin is notably preferred to gabapentin, due to its better pharmacokinetic profile [66-70]. More studies should be necessary to test the varying efficacy of these medications for CIPN treatment. Few but convincing studies, demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs), represent the best treatment for CIPN [71]. According to current guidelines, Duloxetine, a selective serotonin and norpholedrine reuptake inhibitor (SNRI), is the only recommended agent for painful neuropathic symptoms, as confirmed by many studies [72-75]. A large, randomized trial demonstrated a moderate clinical benefit in patients with painful CIPN treated with duloxetine versus placebo, with a higher rate of pain reduction (59% versus 38%) [17].

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Alternatively, a small, randomized trial supports the use of Venlafaxine [18]. No successful studies revealed the efficacy of Tricyclic antidepressants (TCAs) for the treatment of pain associated with CIPN. Moreover, TCAs possess many side effects and thus they should be avoided because they would put the patient's life at risk [76-78]. Regarding the antioxidants, different studies demonstrated that mangafodipir, by inhibiting the production of ROS and the consequent cascade of events causing CIPN, can counteract CIPN, although is not yet commercially available [79-81]. Opioids can be used as salvage therapy for CIPN [82-83]. Interestingly, emerging studies highlighted a potential role of cannabinoids (i.e.nabiximols) in CIPN treatment [84-87], although additional studies should be necessary to identify not only their efficacy but also their safety for treated patients. Studies performed with other drugs such as the amino acid glutamine gave discouraging results [88-90]. Non-pharmacological approaches such as scrambler therapy, acupuncture, and exercise may reduce established CIPN symptoms and appear to be reasonably safe [21].

Despite several pharmacological agents have been studied for CIPN prevention, no agent has demonstrated efficacy and no positive recommendation exists in this setting. Interestingly, Calmangafodipir (PledOx) a low molecular weight superoxide dismutase mimetic (LowMEM) compound derived from mangafodipir has shown preliminary activity in CIPN prevention.

A BALB/c murine model showed a protective effect of calmangafodipir against OHP-induced small fiber neuropathy. Interestingly, a U-shaped effect was observed with higher doses less effective than the lower doses. In a phase I-II trial, Calmangafodipir at a dose of 5 mmol/kg reduced the development of oxaliplatin-induced acute and delayed CIPN without apparent influence on tumor outcomes. Recent data show that the Sigma-1 receptor plays a key role in neuroprotection against chemotherapy-induced peripheral neuropathy. S1R is a transmembrane protein in the endoplasmic reticulum, at the mitochondria-ass endoplasmic reticulum membrane. MR309, a novel selective sigma-1 receptor ligand previously developed as E-52862 was tested in phase II, a randomized placebo-controlled trial. Treatment with MR309 was associated with significantly lower severe chronic neuropathy and with a higher oxaliplatin cumulative dose. [91-94]. Moreover, recent studies demonstrated that neurofeedback therapy (NF), a type of treatment targeting brain activity, alleviates the symptoms of chronic pain, thus representing a putative therapeutic choice for CIPN treatment [95]. Unfortunately, limited data is available and more studies are necessary to determine the clinical utility of these approaches in the treatment of established CIPN.

4. Future therapeutic perspectives

The ceramide-to-S1P rheostat is emerging as a critical regulator of the pain pathway. The functional significance of genetic variations within the ceramide-to-S1P rheostat is object of further investigations to gain a better understanding of neuropathic pain pathogenesis. In this context, FTY720 (fingolimod, Gilenya®), an S1P receptor modulator, the first FDA-approved medicine as an orally bioavailable drug for treating relapsing forms of multiple sclerosis, has raised hopes for treating neuropathic pain disorders. Fingolimod, is currently being investigated in several trial for management of CIPN [22]. Erythropoietin-Producing Hepatoma Receptor A (EPHA) genes encode for receptors associated with neural development and nervous system repair. Gene variants in EPHA 5, 6, and 8 have been associates with increased risk for taxane-induced CIPN. In addition, Single nucleotide polymorphisms (SNPs) in VAC14, a neurodevelopmental protein, have been associated to docetaxel-induced CIPN. Future trials

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should adopt a multimodal methodological approach, with the implementation of subjective (patient-reported) outcomes as primary endpoints and objective (neuro-physiological; imaging) outcome as secondary endpoints, to reveal the full extent of CIPN abnormalities, their impact on patient's function and quality of life and to dive insights into the pathophysiology of symptomatic CIPN (**Figure 2).**

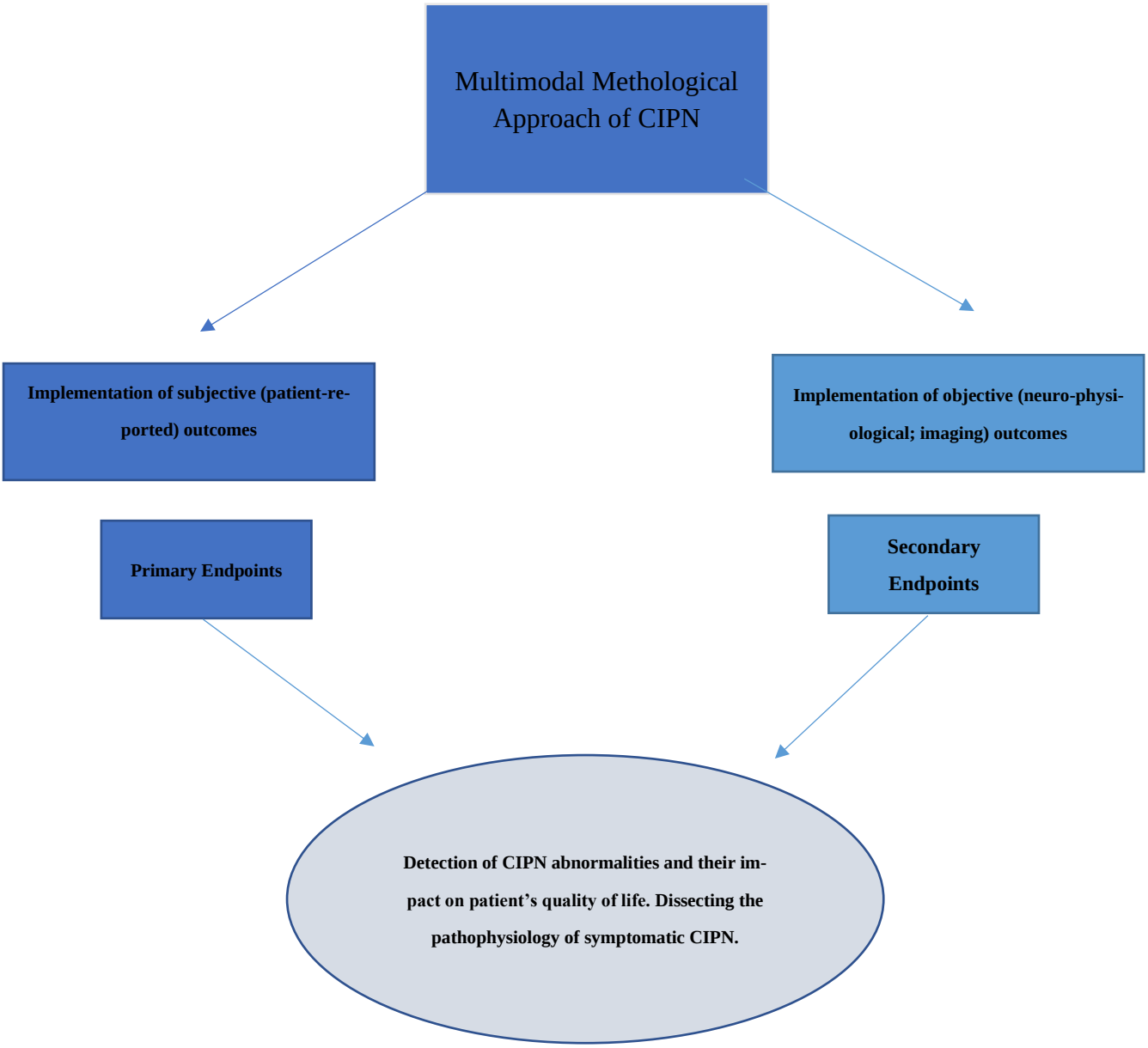

Figure 2. Multimodal methodological approaches of CIPN. The multimodal methodological approach should provide the implementation of subjective (patient-reported) outcomes as primary endpoints and objective (neuro-physiological; imaging) outcomes as secondary endpoints, to reveal the full extent of CIPN abnormalities, their impact on patient's function and quality of life and to dive insights into the pathophysiology of symptomatic CIPN.

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5. Conclusions

Chemotherapy-induced peripheral neuropathy (CIPN) arises as a challenging nerve-damaging adverse effect of chemotherapy used for cancer treatment. The disorder may require a dose reduction of chemotherapy and is accompanied by multiple sensory symptoms, thus affecting dramatically the patient's quality of life (QoL). Moreover, CIPN is difficult to be assessed and diagnosed. Its pathophysiology is very complex and is featured by underlying mechanisms not completely known. Many pharmacological and non-pharmacological therapeutic approaches have been tested in pre-clinical and clinical studies, to overcome these symptoms, but unfortunately, no standardized cure, except those based on duloxetine, to prevent or treat CIPN, is available. Despite encouraging results being obtained by using different therapeutic approaches (i.e. cannabinoids, fingolimoid, physical therapy, etc.), further clinical studies will be needed to test not only the efficacy but also the safety of patients suffering from CIPN. Future strategies should be based on a multimodal methodological approach with the implementation of subjective and objective outcomes, to highlight the CIPN anomalies, their impact on patient's function and quality of life, and dive insights into CIPN pathophysiology.

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