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Drug-Induced Peripheral Neuropathy: Focus on Newer Offending Agents

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Abstract

Peripheral neuropathy (PN) is a common neurological disorder resulting from peripheral nerve damage, significantly contributing to morbidity and adversely affecting patients' quality of life. Drug-induced peripheral neuropathy (DIPN) accounts for 2-4% of cases and typically manifesting as distal, symmetrical sensory polyneuropathy. The growing diversity of medications complicates DIPN diagnosis, often leading to underreporting and mismanagement due to overlapping symptoms with other conditions. This systematic review analyzed DIPN literature up to September 15, 2024, emphasizing both established and emerging neurotoxic drugs. A focused search prioritized recent studies and case reports on new agents, such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs). Traditional chemotherapeutics and other recognized drug classes were summarized, while TKIs and ICIs were analyzed in detail, highlighting their neurotoxic risks. Statistical data on the incidence rates of TKI- and ICI-related neuropathy are not yet uniformly collected or thoroughly analyzed in the literature. Current evidence suggests that incidence rates for neuropathy vary by drug and cancer type, estimated at 10% for TKIs and 14% for ICIs. Increased vigilance is recommended for healthcare providers when prescribing medications associated with PN, particularly newer agents. Regular monitoring and reporting of suspected cases to pharmacovigilance systems are essential for improving patient outcomes and enhancing the understanding of DIPN mechanisms. Further research is necessary to explore neuroprotective strategies and genetic susceptibility factors, enabling personalized treatment appraoches.

Keywords: Drug induced neuropathy, Peripheral neuropathy, Neuropathy with systemic drugs, Chemotherapy-induced neuropathy, Platinum drugs, Taxanes, Vinca alkaloïds, Tyrosine kinase inhibitors, Immune checkpoint inhibitors

Background

Peripheral neuropathy (PN) is one of the most common neurological diseases, with an estimated prevalence of 2.4% in the general population and increasing to 8% in the elderly [1]. PN results from damage to peripheral nerves [2-5]. Although fatal outcomes due to PN are rare, it significantly contributes to morbidity, with pain symptoms affecting 10%–30% of patients and falls and fractures occurring in 18%–25% of adults, adversely affecting patients' quality of life [5-7]. The severity of PN varies depending on the type and distribution of the affected nerves [5]. PN has numerous causes, including diabetes, human immunodeficiency virus (HIV) infection, alcohol abuse, and certain medications [3,8].

Drug-induced peripheral neuropathy (DIPN) is relatively uncommon, accounting for only 2–4% of cases referred to neurology clinics [9-11]. However, broader epidemiological studies estimate that drugs may contribute to up to 24% of all peripheral neuropathies. This discrepancy highlights the under-recognition of DIPN, likely due to the challenges associated with its diagnosis [12]. The majority of DIPN cases present as distal, symmetrical, predominantly sensory polyneuropathy, with dying-back axonal degeneration being the most frequent type of neuropathy linked to medications. Certain drugs, however, can also affect other components of the peripheral nerve, such as myelin, autonomic nerves, and nerve roots [9,13,14]. DIPN can cause severe symptoms and limit the use of medications in about 30% of cases [12].

The number of medications continues to grow rapidly, with over 200 drugs reported to cause neuropathy to date,

although objective evidence is lacking for several [15,16]. A significant challenge in managing DIPN is its underestimation, as subclinical or unsuspected cases often go undiagnosed. Studies suggest that subclinical cases may account for 60 to 90% of all DIPN [12]. Additionally, many cases are managed internally and not referred to neurologists, leading to underreporting. Furthermore, mild neuropathic symptoms are frequently overshadowed by more serious underlying conditions, notably malignancies and HIV infection [11,15].

Diagnosing DIPN is particularly challenging due to the lack of a definitive test to identify the causative medication. The difficulty is compounded when neuropathy develops gradually, with symptoms appearing months or even years after the initiation or dosage adjustment of the drug [15]. Recognizing these drug-related cases is essential, as it may prevent unnecessary, costly or invasive investigations. Moreover, early intervention, including timely discontinuation of the offending drug, can help limit toxicity and potentially lead to complete resolution of symptoms in 50%–70% of cases when identified early [11,15-18].

This review aims to provide a comprehensive overview of the literature on drug-induced peripheral neuropathy, with a particular focus on emerging medications that are newly implicated as triggers.

Methodology

We conducted a systematic review of the literature using PubMed to identify articles on drug-induced peripheral neuropathy published up to September 15, 2024. The search strategy employed the following key terms: "neuropathy", "peripheral neuropathy", "drug-induced", "neurotoxicity" and "axonal neuropathy".

Based on the initial search results, additional searches were performed using terms such as 'chemotherapy', 'proteasome inhibitors', 'anti-tumour necrosis factor-alpha', 'statins', 'targeted therapy', 'tyrosine kinase inhibitors', 'immunotherapy', 'immune checkpoint inhibitors', 'interferon', 'antibiotics', and 'fluoroquinolones'.

Inclusion criteria

- Articles published in English that focused on original studies, reviews, case series and case reports were included.
- Preference was given to articles published within the last ten years for current insights.
- Studies on established drug classes, such as chemotherapeutic agents, cardiovascular drugs, and antimicrobials, were summarized.
- Newer agents, including tyrosine kinase inhibitors and immune checkpoint inhibitors, were discussed in detail.

Exclusion criteria

- Articles lacking original data were excluded.
- Search terms for 'Guillain-Barré syndrome' and 'optic neuropathy' were omitted.
- Articles focusing only on Guillain-Barré syndrome or optic neuropathy were excluded, unless these conditions were directly linked to the drugs of interest (tyrosine kinase inhibitors and immune checkpoint inhibitors).

To facilitate the presentation and interpretation of data, findings are organized into the following tables :

- **Table 1:** Summarizes key characteristics of well-known drug classes that induce peripheral neuropathy such as incidence, risk factors, type of neuropathy, primary symptoms, management options, clinical outcomes, and potential mechanisms.
- **Table 2:** Focuses on cases of neuropathy linked to tyrosine kinase inhibitors (TKIs), highlighting agent-specific variations.
- **Table 3:** Details cases of neuropathy linked to immune checkpoint inhibitors (ICIs), emphasizing variations among different agents.
- **Table 4:** Provides a comprehensive list of drugs identified in the literature as potential causes of peripheral neuropathy, forming an up-to-date reference for clinicians and researchers.

Results and Discussion

Pathogenesis of drug-induced peripheral neuropathy

The exact etiology of DIPN remains largely unknown; however, several potential mechanisms have been proposed [3,7,10,11,19-21] **(Figure 1)**:

Direct mechanisms

- Disruption of axonal transport: leading to axonal degeneration

Indirect mechanisms

- Oxidative stress and mitochondrial dysfunction: Caused by inhibiting DNA polymerase gamma or blocking mitochondrial protein synthesis.
- Vitamin deficiencies: Vitamin B1 (Thiamine), B6 (Pyridoxine), B12 (Cobalamin), and B9 (Folate).
- Drug-induced peripheral nerve vasculitis.
- Alteration of ion channel activity: which disrupts normal nerve function.

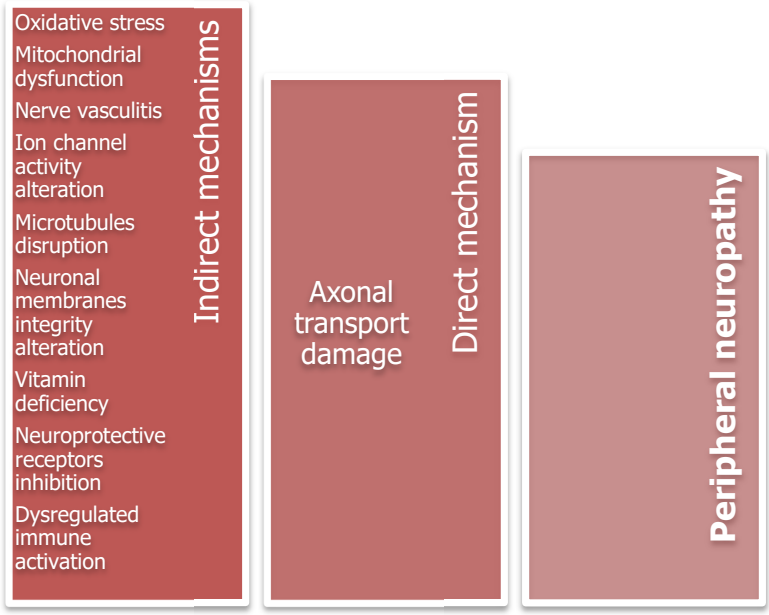

Figure 1. Mechanisms of drug-induced peripheral neuropathy.

- Immune-mediated processes and neuroinflammation: that involve inflammatory responses affecting nerve tissue.

- Interference with microtubules: altering axon structure and function.

Culprit drugs

Chemotherapeutic drugs: PN is a common adverse effect of various chemotherapeutic agents, causing significant pain and discomfort in cancer patients. Approximately 68% of patients undergoing chemotherapy experience PN within the first month of treatment. Chemotherapy-induced peripheral neuropathy (CIPN) is a well-documented toxicity that frequently necessitates dose reduction or discontinuation of the offending agent, often resulting in the use of less effective alternatives [11,19,22].

PN is associated with six major groups of chemotherapeutic agents. The highest incidence has been identified with platinum-based drugs (70–92%), vinca alkaloïds, particularly vincristine (96%), taxanes (up to 76%), thalidomide (23–70%), proteasome inhibitors like bortezomib and epothilones such as ixabepilone (64%) [10,11,19,23] **(Table 1)**.

CIPN may present acutely, either during or shortly after infusion, particularly with agents like oxaliplatin and paclitaxel. More commonly, it manifests as a delayed effect following high cumulative doses [19]. CIPN is predominantly sensory and initially targets long axons. It typically presents with progressive symptoms such as numbness, tingling, and paresthesias in the distal limbs, along with impaired vibration and altered touch sensations. Pain is common, affecting up to 80% of patients [23]. In severe cases, loss of sensory perception can occur, while motor impairment is less frequent. Autonomic symptoms are primarily associated with vinca alkaloids [23].

Platinum-based compounds: Among platinum compounds, carboplatin is generally less neurotoxic than cisplatin and oxaliplatin, but can still cause severe neurotoxicity at standard doses [21]. Platinum-based agents often exhibit long-term manifestations of neuropathy, including the development of chronic neuropathy due to drug accumulation in the dorsal root ganglion. They are also associated with the "coasting" phenomenon, where neuropathy may continue to progress for several months after therapy cessation. Additionally, symptoms may occasionally emerge up to three weeks after treatment has ended [10,11,19] **(Table 1)**.

Vinca alkaloids: Among vinca alkaloids, vincristine is associated with the highest incidence of neurotoxicity, although vinorelbine and vinblastine have also been reported to cause PN. Unique to this class, vinca alkaloid-induced PN can present with unusual manifestations including autonomic dysfunction in up to one-third of patients, as well as less commonly occurring mononeuropathies and cranial nerve palsies [10,11,19]. These drugs affect microtubule dynamics, leading to alterations in the neuronal cytoskeleton and axonal transport. Vincristine, with its highest affinity for tubulin, produces the most severe neuropathy. In contrast, neuropathy associated with other vinca alkaloids is often less severe [21]. Vinorelbine, in particular, causes mild, distal axonal sensorimotor neuropathy, frequently involving deep tendon reflexes (reported in 94% of cases) and paraesthesia in approximately half of cases [21] **(Table 1)**.

Table 1. Key characteristics and features of peripheral neuropathy associated with major drug classes.

Drug	Incidence	Risk factors	Dosage	Time of onset	Type of neuropathy/main symptoms	Management and outcome	Mechanism
Platinum compound: Oxaliplatin [11,19,20]	90%	- Exposure to cool temperature - Cumulative dose - Low body weight - Body surface area >2	60 mg/m^2	- Few days	- Cold hypersensitivity: jaw tightness, cramps, perioral and limb paresthesias - Tetanic spasms, fasciculations, muscular contractions	- Decline between treatment cycles - Resolution within hours or days	- Channelopathy: alteration of ion channel activity in particular calcium homeostasis - Excessive neuronal excitation - Mitochondrial dysfunction and oxidative stress - Neurodegeneration
	70%	- Young age - Persistent neuropathy in a past cycle - Recent surgery	>540 mg/m^2		- Chronic sensory neuropathy: tactile allodynia and numbness, paresthesias, hypoesthesias and dysesthesias of the hands and feet - Changes in proprioception (>780 mg/m^2)	- Complete resolution within 6–8 months in 40% of patients	
Cisplatin [19]	92%	- Cumulative doses - Long time of exposure	540–600 mg/m^2)	- From the 1st to the 12th cycle of therapy	- Acute: tingling, numbness, mechanical and thermal hyperalgesia	- Coasting phenomenon*	- Changes to calcium homeostasis and cell signaling - Mitochondrial dysfunction - Changes in voltage-dependent Na^+ channels resulting in oxidative stress
	5–20%			12 months	- Chronic neuropathy		- Damage to dorsal root sensory neurons mediated by irreversible cross-linking to DNA and neuronal apoptosis
Taxanes: Paclitaxel [10,19,20]	30% 70-95%	- Increased frequency - Cumulative dose	300 mg/m^2			- Resolution within 6 months	- Ion channel dysfunction - Demyelination and axonal degeneration - Immune-mediated processes - Mitochondrial dysfunction
Docetaxel [10,19,21]	Up to 50%	- Increased frequency - Cumulative dose	100 mg/m^2			Improvement or complete resolution within 6 months	

Vinca alkaloids: Vincristine [10,11,19,28]	96% of patients with incidence rates ranging from 0% to 37% for grade 3 or 4	- Older age - Higher single dose and cumulative drug concentration - Concurrent administration with azoles antifungals	>4 mg/m^2	Several weeks	- Sensory, motor and autonomic components - Decreased touch, vibration, and temperature sensations - Reduced or absent ankle reflexes - Initially in the distal lower extremities and progresses proximally	- Coasting phenomenon* - Complete recovery	- Disruption of calcium homeostasis - Immune-mediated processes and neuroinflammation - Membrane remodeling of peripheral neurons - Loss of large myelinated fibers - Polymerization dysfunction within axonal microtubules
Anti-myeloma treatment: Thalidomide [10,11]	23-70% (with up to one-third grade 3–4)	- High doses - Duration of exposure	>200 mg/ d		- Painful sensory length-dependent axonal neuropathy: numbness, paresthesias, cramps - Mild motor dysfunction	- Resolution	- Nuclear factor-dependent dysregulation of neurotrophins - Antiangiogenic activities
Bortezomib [10,11]	37%-64% (with 13% grade 3 or 4)	- Cumulative dose - Longer treatment duration - Combination therapy with thalidomide	30 mg/m^2	5th cycle	Length dependent sensory neuropathy of small c-fiber: significant burning pain, distal paresthesia, numbness - Motor involvement (severe cases) - Autonomic neuropathy (15% of cases): diarrhea, constipation, orthostatic hypotension	- Resolution in 85% within a median of 98 days	- Nuclear factor-dependent dysregulation of neurotrophins - Promotion of mitochondrial calcium release and interference with microtubule stabilization - Activation of ATF3 in DRG and neurodegeneration
Epothilones: Ixabepilone [10,16]	15%-64%	- High dosage - Duration of infusion - Cumulative dose	>40 mg/m^2	4 cycles	Sensory neuropathy	- Dose reduction is effective - Mostly reversible	- Microtubule dysfunction
Arsenic Trioxide [10]	10.3%		10 mg/d		- Chronic sensorimotor polyneuropathy	- Mild and reversible	- Acute axonal damage with demyelination - Thiamine deficiency
Statins [10,11,21,31]	21% (OR of 1.19 to 4.6)	- Duration of treatment (>2 years)		1- 5 years	- Sensory neuropathy: decreased vibration perception	- May persist for months or years after statin withdrawal but often reversible	- Alteration of membrane function - Hypersensitivity and immune-mediated processes - Disruption of ubiquinone synthesis and change in neurons' energy consumption

Amiodarone [10,11,21]	6-10% (2.38 per 1000 person-years)	- Increased dose - Duration of therapy	>200 mg (at maintenance dose of 600 mg/d)	> 1month	- Subacute or chronic symmetrical sensorimotor neuropathy which progress to involve proximal muscles resulting in quadriplegia - Acute resembling GBS (rare)	- Resolution or persistent disability if severe axonal loss	- Oxidative stress and impaired lysosomal degradation within Schwann cells - Lipophilic nature and accumulation in tissues - Demyelination and axonal degeneration by accumulation of amiodarone and its metabolite desethylamiodarone
Isoniazid [10,27]	2-44%	- Increased dose - Alcohol dependence - Malnutrition -diabetes - HIV infection - Elderly and pregnant	16-25 mg/ kg/day	3-5 weeks	Sensory	-Supplementation with pyridoxine - Resolution within weeks to months	- Interference with vitamin B6 synthesis
Ethambutol [10,27]	1-18%	- Increased dose - Eldery - Prolonged duration of treatment - Hypertension - Renal failure - Diabetes - Concurrent optic neuritis - Tobacco and alcohol	> 15 mg/kg/ day	>2 months	Optic: bilateral vision loss	Mostly reversible	- Zinc chelation affecting mitochondrial metal-containing enzymes - Excitotoxic pathway activation - Mitochondrial dysfunction
Linezolid [10,11,27]	13-20%	- Prolonged treatment - Increased doses		>1 month	- Sensory - Optic	Irreversible	- Protein inhibition - Mitochondrial toxicity
Fluoroquinolones [3,4,44]	Increased relative incidence of neuropathy of 1.47	- Additional day of exposure		4 days	- Mono and polyneuropathy: burning sensation, pain		

Metronidazole [10, 21]	10-85%	- Prolonged treatment - Increased dose		4-11 months	Motor, sensory, autonomic and optic neuropathy	Recovery	binding to neuronal RNA and axonal degeneration
Azoles antifungals [10,28]	11.7% Voriconazole (9-30%) Itraconazole (17%) Posaconazole (2.5%)	- Increased doses - Diabetes	150-350 mg	3 months	- Bilateral symmetrical sensory axonal, and typically small fibers affected the earliest: tingling, numbness, decreased position and vibratory sensation, - Motor neuropathy reported with voriconazole: weakness	- Complete recovery within few weeks - Irreversible in minority	- Caused by the azole group - Mitochondrial destruction
Antiretroviral Drugs [10,11]	8-10% (Zalcitabin: 30-100% Didanosine: 23% Stavudine: 31% Lamivudine: rare	- Advanced HIV disease - Older age - Metabolic impairements - Pre-existing neuropathy - Underlying malignancy - Low CD4 count <50 cells/mm^3 - Increased doses - Combination therapy - Alcohol use	Zalcitabine: 2.25 mg/day Didanosine: 400 mg/day Stavudine: 30-40 mg Lamivudine: 300 mg/day	1 week to 6 months	Distal axonal sensory small fiber neuropathy: burning, shooting pain, allodynia, numbness, altered thermal sensitivity, uncomfortable walking distal weakness, decreased ankle jerk reflex	Difficult management	-Inhibition of γ-DNA polymerase leading to mitochondrial dysfunction
Tumor Necrosis Factor alpha inhibitors [10,11,32,80]	0.003%	- Increased dose - Prolonged duration of treatment		6 weeks -2 years (mean of 8 months)	- GBS - MFS - CIDP - Multifocal motor neuropathy - Mononeuropathy multiplex - Axonal sensorimotor polyneuropathy	Significant response to IVIg, plasmapheresis or corticosteroids and dose reduction in some patients - Improvement over few months of drug cessation - Spontaneous relapse can occur	- Inhibition of the proinflammatory role of TNF-a - T cell and humoral immune attack on peripheral myelin - Vasculitis-induced nerve ischemia - Inhibition of axon signaling

Interferons [10, 80]	Rare	Concomitant autoimmune disease			- Axonal and demyelinating neuropathy - Autoimmune polyradiculopathy - Chronic inflammatory demyelinating polyneuropathy -Focal neuropathy at interferon β injection sites in the radial nerve distribution	- Plasmapheresis or IVIg - Recovery	- Immune-mediated myelin degradation - Vessel occlusion leading to nerve ischemia - Induction of anti-GM1 antibodies
Leflunomide [10,16]	5-10%	- Older age - Diabetes - Previous use of neurotoxic drugs - Alcoholism		3 to 6 months	Distal axonal sensorimotor polyneuropathy	Slow recovery	- Neurologic vasculitis - Epineural perivascular inflammation
Levodopa [10,31]	20-55% (30.2%)	- Increased dose - High serum Hcy - Low vitamin B12 - LCIG administration - Low BMI	700 mg/day (higher risk > 1500 mg/ day)	>3 years	Axonal sensory neuropathy: mildly symptomatic or even asymptomatic, slowly progressive	Vitamin supplementation in particular vitamin B12	-Accumulation of Serum homocysteine and cobalamin-related metabolites - Free radical accumulation
Anti-epileptic drugs [30]	16.7% with different agents 12%-14% (TPM)	Combined therapy	Toxic and non toxic doses (PTH)	Short and long term treatment (PTH)	- Axonal sensory: stocking hypesthesia, reduced achilles reflexes - Demyelinating and axonal (TPM): transient parasthesia in the face, mouth and extremities, parathesia in both lower limbs, decreased ankle jerks		- PHT: direct toxic effect or blockage of sodium channels - TPM: inhibition of carbonic anhydrase isoenzymes

*Symptoms may persist for several months despite drug cessation and can progressively worsen over time; DRG: Dorsal Root Ganglia; OR: Odds Ratio; GBS: Guillain–Barre Syndrome; HIV: Human Immunodeficiency Virus; MFS: Miller Fisher Syndrome; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; ATF3: Activating Transcription Factor 3; IVIg: Intravenous Immunoglobulin; TNF: Tumor Necrosis Factor; Hcy: Homocysteine; LCIG: Levodopa-Carbidopa Intestinal Gel Infusion; BMI: Body Mass Index; PTH: Phenytoin; TPM: Topiramate.

Taxanes: Paclitaxel is more frequently associated with PN compared to docetaxel; however, docetaxel tends to induce more severe neuropathy. Both taxanes disrupt microtubule dynamics and alter axonal transport, with neuropathy being more prevalent in dose-dense regimens. Approximately 71% of patients receiving taxanes develop delayed neuropathic symptoms, although some may also experience acute painful neuropathy, which typically peaks a few days after infusion [10,11,19] **(Table 1)**.

Proteasome inhibitors: Similar to other types of antineoplastic agents, proteasome inhibitors are associated with PN, which is a significant dose-limiting toxicity that can curtail their effectiveness. To reduce the toxic profile of bortezomib, the first proteasome inhibitor approved for clinical use, a new generation of structurally distinct proteasome inhibitors has been developed and is increasingly used in clinical settings. Second-generation proteasome inhibitors, such as carfilzomib and ixazomib, demonstrate a significantly lower incidence of PN compared to bortezomib. Notably, ixazomib exhibits the lowest incidence of PN among these agents, and when it occurs, it is generally mild, with most affected patients having reported prior exposure to bortezomib [24,25,26] **(Table 1)**.

Epothilones: Epothilones are utilized in the treatment of advanced breast cancer and include both natural agents and the semisynthetic analogue, ixabepilone. These agents bind to tubulin at distinct sites, akin to vinca alkaloids and taxanes. PN associated with ixabepilone is primarily characterized by mild to moderate sensory neuropathy, which improves after drug withdrawal. More severe cases are rare when ixabepilone is used in monotherapy but occurs in 10% to 15% of patients receiving combination therapy or those previously treated with taxanes or capecitabine. The reported reversibility of epothilone-induced neuropathy is notable, especially in contrast to experiences with other microtubule-targeting agents [16,21] **(Table 1)**.

Other antineoplastic drugs: Arsenic trioxide, used in the treatment of acute leukaemia, has also been associated with PN. Many newer microtubule-binding agents, including eribulin and cabazitaxel, are linked to PN. Cabazitaxel has also been associated with optic neuropathy. Overall, patients treated with these newer agents experience a lower frequency and severity of neuropathy compared to those receiving older treatments. Additionally, brentuximab, an antibody-drug conjugate approved for lymphoma treatment, exhibits a vinca-like mechanism of action on axonal transport, leading to dose-dependant and reversible PN upon drug interruption [21,24] **(Table 1)**.

Antimicrobials

Antibiotics: The antibiotics most commonly associated with PN are metronidazole, linezolid, and dapsone. However, neuropathy has also been described in patients taking chloramphenicol, chloroquine, ethambutol, fluoroquinolones, isoniazid, nitrofurantoin, and sulfasalazine. The mechanism behind antibiotic-induced neuropathy is primarily believed to involve axonal injury resulting from disruptions in DNA repair, cellular metabolism, and mitochondrial function. Antibiotic-induced PN most commonly presents as sensorimotor neuropathies; however, autonomic neuropathy has been observed with metronidazole, while dapsone is linked to pure motor neuropathy. Optic neuropathy is most frequently associated with linezolid and ethambutol, though individual case reports have noted optic neuropathy with other antibiotics including ciprofloxacin, levofloxacin, chloramphenicol, metronidazole, sulfonamides, isoniazid, and streptomycin. Prolonged exposure to antibiotics is a significant risk factor for developing PN. In most patients, recovery occurs within weeks to months after discontinuation of the antibiotics, although "coasting" phenomenon has been described in a few cases [27] **(Table 1)**.

Azole antifungals: The reported incidence of PN in patients treated with azoles varies widely in the literature. PN is most commonly documented when azoles are administered concurrently with vinca alkaloids in patients with hematologic malignancies or with calcineurin inhibitors in transplant recipients. Nevertheless, PN has also been observed following the administration of fluconazole, itraconazole, voriconazole, and posaconazole in the absence of other neuropathy-inducing medications or underlying conditions [28] **(Table 1)**.

Antiretroviral drugs: The incidence of PN with antiretroviral drugs varies by agent and is often cited as a frequent reason for discontinuing therapy. Among these agents, lamivudine appears to have a low incidence of PN compared to others. The clinical symptoms, physical examination findings, and neurophysiological studies associated with this toxic neuropathy due to antiretroviral drugs resemble those seen in distal sensory neuropathy caused by human immunodeficiency virus (HIV) [10,11] **(Table 1)**.

Cardiovascular drugs

Cardiovascular drugs are generally well tolerated and infrequently lead to neurological complications. However, both statins and antiarrhythmics have been associated with a potential risk of developing PN [21].

Statins: Previous studies indicate that while the overall prevalence of PN is low, it is up to four times higher among patients using statins. Statin-related PN can occasionally manifest in rare forms, such as Guillain-Barré syndrome and small fiber neuropathy. Typically, this type of neuropathy resolves after discontinuation of the statin. However, symptoms have been reported to recur either after re-challenge with the same statin or after switching to a different one. Statins interfere with cholesterol production, which is crucial for maintaining the function and integrity of cell membranes, particularly in the peripheral nervous system. By altering

cholesterol levels, these drugs may compromise membrane stability. Additionally, statins inhibit ubiquinone (Coenzyme Q10), a key component in mitochondrial respiration, potentially impacting neuronal energy metabolism and contributing to the development of PN [11,13,21].

Antiarrhythmic drugs: PN has been reported with various antiarrhythmic drugs, often considered a class effect across this drug group, particularly resembling the well documented amiodarone-induced neuropathy. However, data on the relative risk of PN in patients treated with antiarrhythmics remain limited. A 2018 retrospective study found a low PN incidence ~~of~~, ranging from 1.08 per 1,000 patient-years with flecainide to 2.38 per 1,000 patient-years with amiodarone. Amiodarone, in particular, has PN as one of its most frequently reported neurological adverse effects, with several case reports detailing its occurrence. Conversely, fewer than three cases of PN associated with flecainide have been reported in the literature. Amiodarone-induced PN can occur with doses as low as 200 mg/day or within a month of treatment, although the risk increases with higher cumulative doses or prolonged use [11,29] **(Table 1)**.

Nervous system agents

Anti-epileptic drugs: Peripheral neuropathy is a rare but significant adverse effect of anti-epileptic drugs (AEDs). Identified risk factors for AED-induced PN include high doses, elevated serum concentrations, and prolonged treatment duration. Among AEDs, phenytoin (PHT) is most frequently associated with PN, as demonstrated by both clinical and experimental studies. PN can develop during both short-term (hours to weeks) and long-term (≥ 5 years) PHT therapy, regardless of whether the adminisetred doses are therapeutic or toxic [(30)] **(Table 2)**.

Levodopa: Several studies have demonstrated a significant association between PN and dopamine-replacement therapies. Up to 55% of patients treated with oral levodopa and 75% of those receiving l-dopa/carbidopa intestinal gel (LCIG) infusions may develop PN symptoms. A 2019 systematic review reported a PN prevalence of 30.2% in Parkinson's disease patients on oral l-dopa, increasing to 42.1% in those treated with LCIG. Oral l-dopa-related PN typically presents as a slowly progressive axonal neuropathy, primarily affecting sensory fibers. In contrast, LCIG-induced PN often involves both motor and sensory components, with most cases presenting as axonal neuropathy, though 9.2% show demyelinating features. While PN associated with oral l-dopa tends to follow a chronic course, 35.7% of cases linked to LCIG have an acute or subacute onset, suggesting potential immune-mediated inflammatory mechanisms, possibly triggered by the PEG-J tube or the gel formulation. Other factors, such as neurodegeneration, toxic exposures, or nutritional deficiencies, may also contribute to the development of acute PN in LCIG-treated patients. Neurophysiological findings often indicate axonal patterns, and the frequent co-occurrence of vitamin B12 deficiency further supports this. Notably, vitamin B12 deficiency-induced PN can share clinical features with LCIG-associated PN [31].

Immunosupressive drugs

Various classes of immunosuppressive drugs, such as tumor necrosis factor-alpha (TNF-α) inhibitors, interferons, calcineurin inhibitors, and leflunomide, have been linked to the development of PN [10].

Tumor necrosis alpha inhibitors: TNF-α inhibitors have been associated with a range of neurological complications, including central nervous system demyelination, optic neuritis, and various forms of neuropathy. Evidence on the risk of PN with TNF-α inhibitors primarily comes from case reports and series, although several reviews have confirmed these associations. PN has been reported with infliximab, adalimumab, and etanercept, with fewer cases linked to certolizumab. Notably, no neuropathies have been observed with the newer golimumab. Typically, PN develops shortly after the initiation of anti-TNF-α therapy and often improves with treatment withdrawal. Management strategies include corticosteroid use, dose reduction of the anti-TNF-α agent with low-dose corticosteroids, or complete drug discontinuation. However, some patients experience relapses months after treatment cessation, underscoring variability in clinical outcomes [9,11,32].

Calcineurin inhibitors: Calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine, are known to cause neurotoxicity, particularly PN [28]. Risk factors for CNI-induced neurotoxicity include elevated plasma concentrations, co-administration of azole antifungals, diabetes, and intravenous administration. Additional risk factors for cyclosporine-treated patients include advanced liver failure, hypertension, hypocholesterolemia, and hypomagnesemia [28]. The incidence of neurotoxicity is slightly higher with tacrolimus than cyclosporine, with PN affecting approximately 3 in 1,000 tacrolimus-treated patients [33]. PN typically presents as multifocal demyelinating sensorimotor polyneuropathy within 2 to 10 weeks of therapy initiation, and symptoms often improve or resolve after discontinuation [34]. CNI-induced PN is thought to involve both calcineurin inhibition and an immune-mediated component [35]. Management options include dose reduction or switching to an alternative CNI. For instance, switching from tacrolimus to cyclosporine may alleviate tacrolimus-induced neurotoxicity, while switching from cyclosporine to sirolimus has been reported to relieve cyclosporine-induced neurotoxicity. The distinct chemical structures of cyclosporine and tacrolimus, despite their shared immunosuppressive mechanisms, likely contribute to the more efficient clearance of tacrolimus and its metabolites [35]. In contrast, sirolimus, which operates through a different mechanism of action, is generally not linked to neurotoxicity and has been shown to mitigate the neurotoxic effects of both cyclosporine and tacrolimus [33].

Table 2. Drugs reported in literature to cause pripheral neuropathy.

Chemotherapeutic drugs	Cardiovascular drugs	Antimicrobials	Nervous system drugs	Immunosuppressive drugs	Other agents
Cisplatin	Amiodarone	Isoniazid	Phenytoin	Etanercept	Chloroquine
Oxaliplatin	Donedarone	Ethambutol	Carbamazepine	Infliximab	Colchicine
Carboplatin	Flecaïne	Linezolid	Phenobarbital	Adalimumab	Allopurinol
Paclitaxel	Procaïnamide	Dapsone	Sodium valproate	Certolizumab	Sulphasalasine
Docetaxel	Disopyramide	Nitrofurantoin	Levetiracetam	Leflunomide	Dichloroacetate
Thalidomide	Propafenone	Metronidazole	Gabapentin	Tacrolimus	Cimetidine
Lenalidomide	Hydralazine	Co-trimoxazole	Lacosamide	Cyclosporin	Clofibrate
Vincristine	Sotalol	Eryhtromycin	Topiramate	Interferon alpha	Zimeldine
Vinblastine	Atorvastatin	Azithromycin	Nitrous oxide		Etretinate
Vinorelbine	Simvastatin	Clindamycin	Levodopa		Penacillamine
Vindesine	Pravastatin	Streptomycin	Chlorprothixene		
Bortezomib	Enalapril	Amoxicillin	Glutethemide		
Ixabepilone	Perhexiline	Chloramphenicol	Phenelzine		
Etoposide	Almitrine	Griseofulvin	Disulfiram		
5-Fluorouracil		Levofloxacin	Amitriptyline		
Cytarabine		Ciprofloxacin	Gangliosides		
Gemcitabine		Norfloxacin	Gluthethimide		
Ifosfamide		Moxifloxacin	Litium		
5-azacytidine		Ofloxacin			
Suramin		Sulfonamides			
Misoidazole		Voriconazole			
Teniposide		Fluconazole			
Hexamethylmelamine		Itraconazole			
Misonidazole		Posaconazole			
		Clioquinol			
		Mefloquine			
		Zalcitabine			
		Didanosine			
		Stavudine			
		Lamivudine			

Interferons : Case studies have suggested a link between interferon therapy and the development of axonal sensory neuropathy, with rare reports of inflammatory demyelinating polyneuropathies. While the exact mechanism remains unclear, interference with neuronal DNA, RNA synthesis, and protein metabolism has been proposed. More likely, interferons elevate pro-inflammatory cytokine levels, potentially triggering autoimmune responses in genetically predisposed individuals. This immune response, driven by molecular mimicry, leads to the mistaken attack on the body's nerve tissue, which may result in acute inflammatory neuropathy [36,37] **(Table 1)**.

Leflunomide: Leflunomide-induced PN has been documented in the literature, typically manifesting around three months after treatment initiation, with an onset range of 45 to 120 days [38,39]. Studies suggest that patients who discontinue leflunomide soon after symptom onset are more likely to experience improvement or full recovery compared to those who continue the drug for more than one month [40]. Carulli *et al.* hypothesized that leflunomide-induced PN may be related to neurologic vasculitis triggered by the drug [38] **(Table 1)**.

Tyrosine kinase inhibitors: PN is a common and often debilitating adverse effect observed during anti-tumor therapies, including both chemotherapy and targeted therapies. While CIPN has been well documented, the rise of targeted therapies, particularly tyrosine kinase inhibitors (TKIs), has brought attention to a new spectrum of drug induced neurotoxicities [41] **(Figure 2)**.

Neurological complications associated with TKIs are relatively rare, but various neuromuscular adverse effects have been reported, mainly neuropathy [42]. PN remains an uncommon adverse effect of TKIs, with incidences rarely exceeding 10% [43]. Case reports have linked several TKIs to PN, including brigatinib, crizotinib, encorafenib, imatinib, ivosidenib, ixazomib, lorlatinib, ponatinib, vemurafenib, and sorafenib [23]. A study on dasatinib reported a 5% incidence of PN, with severe cases occurring in only 0.05% [44]. Imatinib, known for inducing optic neuropathy, targets platelet derived growth factor (PDGF) receptors, and its neurotoxicity may stem from inhibiting these neuroprotective receptors on pericytes, affecting the vascular endothelium, retinal ganglion cells, and optic nerve. Although imatinib generally does not cross the blood-ocular barrier, damage to pericytes may allow its passage [44,45]. Sorafenib, another TKI, has been shown to either induce PN or exacerbate taxane-induced neuropathies when used in combination therapy. Sorafenib-induced PN causes significant neuropathic pain that is often resistant to standard analgesics and may necessitate treatment discontinuation. This neuropathy is linked to vascular endothelial growth factor (VEGF) inhibition, which interferes with VEGF's neuroprotective role on sensory neurons, limiting management options to dose reduction or drug withdrawal [23]. Other TKIs have also been implicated in neurotoxicity. Crizotinib has been associated with optic neuropathy. Sunitinib has been reported in approximately 20 cases of optic neuropathy and has also been linked to Guillain-Barre syndrome in the literature [24,46,47]. Bevacizumab led to severe optic neuropathy in 1.2% of patients, necessitating immediate drug discontinuation [46]. Ceritinib treatment has been linked to neuropathy in 17% of patients. Sensory PN was noted as an adverse effect in phase II trials of cediranib [24,48]. In phase II trial of dovitinib, two patients developed significant neuropathy after the first cycle, requiring dose reduction [49]. Additionally, a possible link between ruxolitinib and PN has been suggested in the literature [50]. Momelotinib has been associated with PN in 46% of patients in a phase II trial [51], and lorlatinib-induced PN occured in 43.7% of cases, with a median onset of 77 days [52]. Tandutinib, in experimental studies,

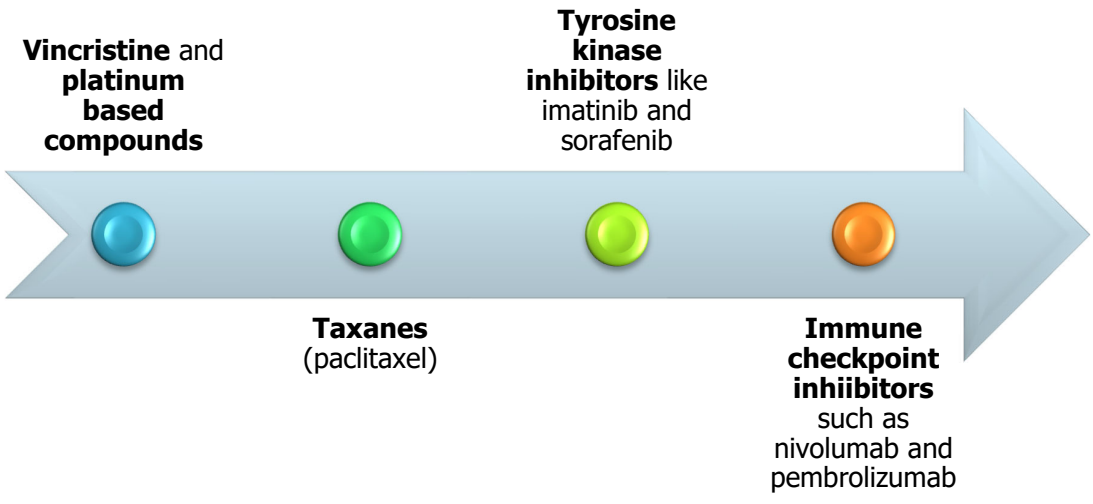

Figure 2. Timeline of Anti-Cancer Therapies induced Peripheral Neuropathy.

caused reversible muscle weakness and electrophysiologic changes consistent with PN [47]. Nintedanib has also been associated with the development of neuropathies [47].

Among patients receiving VEGFR-TKI monotherapy, about 6% experienced neuropathy [53]. Among BRAF and MEK inhibitors, PN is specifically mentioned in the summary of product characteristics for vemurafenib, encorafenib and binimetinib. However, PN is not explicitly listed as known adverse effect for other inhibitors within the same class such as cobimetinib, trametinib and dabrafenib [54]. Regorafenib and encorafenib were linked to PN in 20.1% of cases in the FAERS database [55]. Another recent study indicated that the combination encorafenib and binimetinib increased the risk of PN, with a median onset of around five months, primarily manifesting as axonal sensory neuropathy affecting the lower limbs [54].

According to our literature review, TKI-induced neuropathy predominantly occurs in elderly patients, with a mean age of 56 years and a male predominance (M/F sex ratio = 1.6). A single case of optic neuropathy has been reported in a 14-year-old child [56]. Most cases involved imatinib and dasatinib followed by ibrutinib. Imatinib, the first TKI approved for chronic myeloid leukemia, was later complemented by nilotinib and dasatinib as alternative first-line treatments [57]. Notably, no cases of neuropathy associated with nilotinib were identified, and patients who developed PN on imatinib or dasatinib successfully transitioned to nilotinib [42,43,58,59]. Additionally, one case reported no recurrence of symptoms after switching from imatinib to bosutinib, and no PN cases linked to bosutinib were found [44]. Both axonal and demyelinating nerve injuries have been reported, presenting as sensory or motor symptoms, with optic neuropathy frequently observed. The median onst of symptoms was 3.5 months, ranging from 4 days for motor neuropathy caused by nintedanib [47] to 10 years for sensory neuropathy related to imatinib [43]. Although late-onset neurotoxicity is rare, a delay of up to one year after TKI therapy initiation was observed in several cases involving imatinib [43,58,60,61], dasatinib [44] and ibrutinib [22]. Partial or complete recovery occurred in nearly all cases, and rechallenge with the offending TKI was frequent, often leading to symptom recurrence, although some cases did not experience a relapse upon rechallenge **(Table 3)**.

Table 3. Main characteristics of well-documented neuropathy cases associated with tyrosine kinase inhibitors in the literature.

Author, year	Gender/ Age	TKI agent/ Dosage	Time of onset	Type of neuropathy	Management	Outcome	Rechallenge
Babu, 2007 [81]	M/50	Imatinib 400 mg/d	25 days	Optic neuropathy	Discontinuation Oral prednisolone	Improvement (6 weeks)	None
Breccia, 2008 [82]	F/38	Imatinib 400 mg/d	51 days	Optic neuropathy	Discontinuation Topical steroids	Recovery (6 weeks)	None
Kwon, 2008 [56]	F/14	Imatinib 500 mg/d	2 months	Optic neuropathy	Discontinuation	Improvement (3 weeks)	Negative
Chakupurakal, 2011 [61]	M/58	Imatinib	5.5 years	Sensorimotor neuropathy	Discontinuation	Recovery (6 months)	Positive
Yung, 2011 [83]	M/59	Sunitinib 50 mg/d	18 weeks	Optic neuropathy	Discontinuation	Improvement (2 months)	None
DeLuca, 2012 [84]	M/66	Imatinib 400 mg/d	4 months	Optic neuropathy	Discontinuation	Improvement (few weeks)	Negative with dose reduction
Kunadu, 2013 [47]	F/59	Nintedanib	3 weeks	Motor neuropathy	Discontinuation	Recovery (few weeks)	None
Niro, 2015 [85]	M/70	Vemurafenib + cobimetinib	7 months	Optic neuropathy	Discontinuation	Partial Improvement	None
Monge, 2015 [86]	M/36	Dasatinib 100 mg/d	2.5 months	Optic neuropathy	Discontinuation Oral prednisone	Improvement (2 months)	Switch to nilotinib with no recurrence
Chun, 2015 [87]	F/69	Crizotinib	3 months	Optic neuropathy	Discontinuation	Stabilization	Positive
Napolitano, 2017 [58]	M/62	Imatinib 400 mg/d	1 year	Optic neuropathy	Discontinuation	Recovery (2 months)	Switch to nilotinib with no recurrence

Ishida, 2017[14]	F/46	Dasatinib 100 mg/d	6 months	Demyelinating peripheral neuropathy	Discontinuation Intravenous immunoglobulin	Recovery (1 week)	Positive
Kavanagh, 2018 [43]	F/41	Imatinib 400 mg/d	10 years	Sensory neuropathy	Discontinuation	Improvement (6 weeks)	Positive Switch to nilotinib with no recurrence
Suponeva, 2018 [88]	M/65	Ibrutinib 420 mg/d	5 months	Sensorimotor polyneuropathy	Dose reduction	Improvement	None
Shaikh, 2019 [89]	NS	Ibrutinib	NS	Peripheral neuropathy	Discontinuation	Improvement	None
Rafei, 2019 [44]	M/70	Dasatinib 20 mg/d	7 years	Axonal neuropathy	Discontinuation Intravenous immunoglobulin	Minimal improvement	None
	M/70	Dasatinib 100 mg/d	3 months	Optic neuropathy	Discontinuation Steroids	Partial Recovery	Switch to imatinib with recurrence
		Imatinib 400 mg/d	2 weeks		Discontinuation Steroids	Partial Recovery	Switch to bosutinib with no recurrence
Gun, 2020 [60]	F/59	Imatinib 400 mg/d	2 years	Optic neuropathy	Discontinuation Intravenous methylprednisolone	Recovery (3 days)	Negative
Comert, 2020 [90]	M/63	Ibrutinib 420 mg/d	10 months	Sensory polyneuropathy	Discontinuation	Recovery (4 weeks)	Positive but less severe
Inoue, 2020 [59]	F/54	Dasatinib 100 mg/d	2 months	demyelinating peripheral neuropathy	Discontinuation	Recovery (2 weeks)	Switch to nilotinib with no recurrence
Na, 2021 [83]	M/60	Sunitinib 37.5 mg	1 month	Optic neuropathy	Discontinuation Intravenous methylprednisolone	Improvement	None
Monga, 2021 [45]	F/41	Imatinib 400 mg/d	1 month	Optic neuropathy	Discontinuation	Recovery (3 months)	None
	F/54	Imatinib 400 mg/d	6 months	Optic neuropathy	Discontinuation	Stabilization (1 year)	None
Kunadu, 2021 [47]	M/39	Nintedanib 300 mg/d	4 days	Motor polyneuropathy	Discontinuation	Recovery (2 weeks)	None
Tiwari, 2023 [22]	M/70	Ibrutinib 420 mg/daily	28 months	Sensorimotor neuropathy	Discontinuation	Improvement (1 month)	None
Cellini, 2023 [91]	M/75	Ibrutinib 420 mg/d	9 months	Demyelinating polyneuropathy	Discontinuation Intravenous steroids	Recovery (1 year)	None
Heard, 2024 [92]	M/73	Imatinib	NS	Axonal neuropathy	Discontinuation Methylprednisolone	Improvement (6 weeks)	None

TKI: Tyrosine Kinase Inhibitor; NS: Not Specified

The underlying mechanisms of TKI-induced neuropathy are not fully understood, but studies suggest that toxic metabolite accumulation in mitochondria and the endoplasmic reticulum, which plays a role in TKI-induced cardiotoxicity, may similarly contribute to neurotoxicity [61]. In some cases, an immune-mediated process has been proposed, as seen in dasatinib-induced PN, where patients responded well to intravenous immunoglobulin therapy, suggesting the involvement of auto-antibodies targeting Schwann cells or nerve myelin [14].

Immune checkpoint inhibitors: The advent of oncological immunotherapy has undoubtedly revolutionized cancer treatment, offering long-lasting tumor responses and improved survival outcomes. However, it has not spared patients from potential adverse effects, including PN. This immunotherapy-induced neuropathy is now recognized alongside the well-known toxic neuropathies caused by traditional chemotherapies [2] **(Figure 2)**. Although PN associated with immune checkpoint inhibitors (ICI) are less common than those caused by chemotherapeutics [41], they still pose a significant risk, with reported incidence rates ranging from 3.8 to 12%, and severe reactions occurring in about 1% of patients [62]. Among ICI-induced neurotoxicities, PN is one of the most commonly observed, comprising almost half of all cases in some studies [63] and emerging as the second most reported neurological complication in the European pharmacovigilance database [2]. Recent data suggest the frequency of ICI-related PN is increasing, ranging from 1 to 6% in monotherapy and up to 14% in combination therapies [63,64].

The clinical presentation of ICI-induced PN can be highly variable, manifesting with symptoms such as paresthesia, hyporeflexia, neuropathic pain, muscle weakness, and involvement of cranial nerves [63]. In contrast to CIPN which tends to be symmetric and progressive sensory neuropathy, ICI-related PN is typically asymmetric, with acute onset and notable motor involvement [63]. The management of ICI-induced neuropathy largely depends on its severity. For mild (grade 1) cases, treatment can be continued with close monitoring. Moderate (grade 2) cases require temporary discontinuation of ICI with a possible rechallenge after symptom recovery. Severe (grades 3 or 4) neuropathies warrant permanent drug discontinuation, with corticosteroid therapy being the primary choice. Other treatments, such as plasma exchange or immunoglobulin therapy, may be considered in more resistant cases [63,65]. Most patients exhibit favorable outcomes, but fatal events have occurred in about 20% of those with severe neurotoxicities [63].

A prior analysis of ICI safety reports identified more than 700 cases of PN linked to ICI treatment. The majority of these reports involved nivolumab (35.9%), followed by pembrolizumab (26.3%) and ipilimumab (14.8%). Other ICIs were reported less frequently (<10%), with cemiplimab being the least reported, accounting for only 0.1% of cases [66]. Published case reports primarily incriminated nivolumab, followed by ipilimumab and durvalumab **(Table 4)**. Notably, only one case of optic neuropathy linked to cemiplimab has been documented in the literature [67]. The majority of reports involved elderly patients, with a predominance of males, which aligns with our literature review, where the mean age was 62 years, and 10 out of 12 patients were male **(Table 4)**. In the safety reports analysis, 22.2% of ICI-related PNs resulted in unfavorable outcomes. Similarly, two patients from published case reports showed no improvement even after discontinuation of ICIs. Both demyelinating and axonal injuries were observed in this dataset, with demyelinating PNs being more commonly reported. These findings are consistent with published case reports which describe both types of injuries. Interestingly, this safety reports analysis revealed a higher frequency of atezolizumab-induced PN compared to other ICIs [2,68,69]. Our literature review identified two cases of atezolizumab-induced PN, along with one case of optic neuropathy [67,70,71].

The exact mechanism by which ICIs cause neuropathy remains unclear. While T-cells are thought to play a key role in ICI-mediated toxicity, the wide range of immune-related adverse events suggests that other immune cells and cytokines may also contribute to these reactions through multiple mechanisms. Additionally, the abnormal immune activation triggered by this immunotherapy can result in various complications, including demyelination and axonal damage [2].

Management of Drug-Induced Peripheral Neuropathy

A comprehensive approach to managing peripheral neuropathy includes early recognition, pharmacologic interventions, physical therapy, and environmental modifications.

Although effective therapies supported by high-quality evidence are lacking, pharmacological management should primarily address the symptoms of PN, such as neuropathic pain and paresthesia. Medications used for neuropathic pain include amitriptyline, duloxetine, venlafaxine, gabapentin, pregabalin, and opioids. Duloxetine, at doses of 30 to 60 mg daily, has been found to be more effective than a placebo in reducing chemotherapy-induced neuropathic pain. It is the only medication with sufficient evidence supporting its use as the first-line treatment for patients with neuropathic pain. The evidence for other medications is less robust [72]. For PN-associated paresthesia, B complex vitamins (B1, B6, B12), folic acid, and niacinamide may be considered. Recent pain research has shifted towards addressing neuroinflammation as a strategy for managing chronic neuropathic pain. Notably, toll-like receptor-4 (TLR-4) has emerged as a key player in immune system activation, and ongoing research suggests its potential role in alleviating chemotherapy-induced neuropathic pain [73].

Table 4. Key features of published neuropathy cases linked to immune checkpoint inhibitors.

Author, year	Gender/Age	ICI agent/Dosage	Number of last cycle before neuropathy onset	Time of onset after ICI initiation	Type of neuropathy	Management	Outcome	Rechallenge
Wilson, 2016 [93]	M/53	Ipilimumab 3 mg/kg every 3 weeks	NS	4 months	Optic neuropathy	Discontinuation Steroids	Stabilization	None
Thaipisuttikul, 2017 [94]	M/57	Ipilimumab	NS	36 days	sensorimotor polyneuropathy	Discontinuation Steroids	Improvement	None
	M/62	Ipilimumab	NS	1 month	polyneuropathy	Discontinuation Steroids and mycophenolate	Recovery (4 months)	None
Aoki, 2020 [95]	F/85	Pembrolizumab (200 mg) every 3 weeks	5th cycle	3 weeks	Demyelinating neuropathy	Discontinuation Steroids	Improvement (5 months)	None
Kambayashi, 2020 [96]	M/64	Ipilimumab nivolumab	4th cycle	12 weeks	motor axonal neuropathy	steroids	Gradual improvement	None
Bilic, 2021 [97]	M/70	avelumab	4th dose	NS	demyelinating polyneuropathy	Discontinuation	No improvement	None
Yamanaka, 2021 [70]	M/76	atezolizumab	3rd cycle	NS	Demyelinating polyneuropathy	Discontinuation Steroids IVIg	Recovery	None
Cohen, 2021 [71]	M/64	atezolizumab	16th cycle	1 year	sensorimotor neuropathy	Discontinuation IVIg	Rapid improvement	None
Perez, 2021[98]	M/22	nivolumab	1st dose	1 month	Demyelinating polyneuropathy	Discontinuation Steroids IVIg	Recovery (3 months)	None
Scurfield, 2023 [99]	M/62	durvalumab	NS	4 months	Mononeuopathy multiplex	Discontinuation	Recovery (5 months)	None
McCormak, 2023 [100]	F/71	pembrolizumab	NS	1.5 years	Peripheral neuropathy	Discontinuation Steroids	Recovery (1 month)	None
Bonilla, 2024 [63]	M/74	durvalumab	6th cycle	6 months	Mixed axonal polyneuropathy	Discontinuation Steroids	Recovery (72 hours)	Negative

Pietris, 2023 [67]	M/82	atezolizumab	NS	NS	Optic neuropathy	steroids	NS	None
	F/67	pembrolizumab	NS	NS	Optic neuropathy	Steroids, plasmapheresis, immunoglobulin		None
	M/67	ipilimumab	NS	NS	Optic neuropathy	steroids		None
	F/27	ipilimumab	NS	NS	Optic neuropathy	Steroids Plasma exchange		None
	M/65	durvalumab	NS	NS	Optic neuropathy	steroids		None
	M/64	nivolumab	NS	NS	Optic neuropathy	None		None
	F/65	Cemiplimab	NS	NS	Optic neuropathy	steroids		None
Park, 2023 [101]	F/32	Nivolumab (3 mg/kg) every 2 weeks	NS	7 months	Demeyelinating polyneuropathy	steroids	Improvement	None

ICI: Immune Checkpoint Inhibitor; NS: Not Specified; IVIg: Intravenous Immunoglobulin

Another preventive and therapeutic strategy for alleviating neurotoxicity in patients receiving platinum-based chemotherapy is supplementation with vitamins, minerals and antioxidants. Evidence suggests that vitamin B12 may help prevent or reduce the severity of CIPN, although further studies are needed. Historically, peripheral neuropathy induced by isoniazid has been preventable with pyridoxine (vitamin B6) [74]. Vitamin B3 has shown protective effects in animal studies [75]. Vitamin E has been extensively studied as a preventive and therapeutic agent for the toxic effects of platinum-based chemotherapy. Retinoic acid (a metabolite of vitamin A) has also been explored in cisplatin-induced neuropathy in both animal and human studies. Additionally, thiamine pyrophosphate and coenzyme Q10 have been studied for their potential neuroprotective effects [76]. Vitamin D insufficiency has been suggested as a risk factor for CIPN induced by oxaliplatin, bortezomib, and thalidomide. A previous analysis found that vitamin D supplementation helped prevent CIPN [77].

Non-pharmacological treatment options include physical exercise, acupuncture, auricular plaster therapy and cryotherapy. Acupuncture has proven to be safe and effective. Physical exercise can be started early, even when potentially neurotoxic treatmens are initiated, helping reduce the incidence of PN and alleviating symptoms when they occur [78,79].

Strenghts

In this literature review, we provided a comprehensive overview of drugs linked to peripheral neuropathy, drawing from review articles, clinical trials, retrospective studies, and case reports. Our aim was to compile both medications historically known to induce peripheral neuropathy and those newly associated with this condition. While previous reviews have often studied older and newer triggers separately, our review integrates both, offering an up-to-date resource that can serve as reference for physicians when assessing a medication's role in the devlopment of peripheral neuropathy. We have studied almost all aspects of PN from triggering agents to clinical impacts, possible mechanisms and management options. Additionally, we included a review of case reports on peripheral neuropathy induced by tyrosine kinas inhibitors and immune checkpoint inhibitors, providing valuable insights into the characteristics of this emerging adverse reaction. Furthermore, we presented an up-to-date registry of all drugs reported to cause peripheral neuropathy, enhancing the clinical utility of our review.

Conclusion

Based on our review findings, we recommend increased vigilance among healthcare providers when prescribing medications known or suspected to induce PN, particularly newer therapies such as TKIs and ICIs. Regular monitoring for early symptoms of neuropathy is crucial for timely intervention and management. Further research is warranted to explore the underlying mechanisms of neuropathy associated with these agents, as understanding these pathways could lead to better prevention strategies and treatment options. Research into neuroprotective agents needs to be strengthened and better articulated. Furthermore, successful neuroprotective agents should be incorporated into management guidelines, providing clinicians with effective strategies that improve patients' quality of life. Clinicians should also report any suspected cases to pharmacovigilance systems to contribute to a more robust and up-to-date registry of offending drugs. Research studies identifiying genetic factors that may increase patient susceptibility to peripheral neuropathy should be enhanced, allowing for more personalized treatment approaches.

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