

Drug-Induced Peripheral Neuropathy: Diagnosis and Management



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Abstract: Peripheral neuropathy comes in all shapes and forms and is a disorder which is found in the peripheral nervous system. It can have an acute or chronic onset depending on the multitude of pathophysiologic mechanisms involving different parts of nerve fibers. A systematic approach is highly beneficial when it comes to cost-effective diagnosis. More than 30 causes of peripheral neuropathy exist ranging from systemic and auto-immune diseases, vitamin deficiencies, viral infections, diabetes, *etc.* One of the major causes of peripheral neuropathy is drug-induced disease, which can be split into peripheral neuropathy caused by chemotherapy or by other medications. This review deals with the latest causes of drug-induced peripheral neuropathy, the population involved, the findings on physical examination and various workups needed and how to manage each case.

Keywords: Peripheral neuropathy, chemotherapy-induced, taxanes, platinum drugs, vinca alkaloids, proteasome inhibitors, epithelones, eribulin, brentuximab, suramin, nitrous oxide, disulfiram.

1. INTRODUCTION

Peripheral Neuropathy (PN) can be defined as a disease involving the peripheral nervous system. This system includes but is not limited to cranial nerves, spinal nerve roots, spinal nerve ganglia, trunks, and division, along with the autonomic nervous system [1]. Classifying PNs can be done in many ways. The first approach involves classifying PNs as mono-neuropathies, multifocal neuropathies, and polyneuropathies [2]. Another approach would be to classify the disease as axonal, demyelinating or mixed [3]. While some PNs may appear acutely, others may appear over a period of time which is another differentiating factor of causality. Since both motor and sensory nerve fibers along with the autonomic fibers are involved, PN can have a broad range of presentations and severity. Some of the most common manifestations of PN might be confusing in detecting the cause of disease, however the origin of PN can most of the times be rooted in metabolic, systemic and toxic causes. In a few cases, there might be an idiopathic cause as well. The three main pathophysiological mechanisms which are known to cause PN are segmental demyelination, axonal degeneration and Wallerian degeneration [2]. To note, the latter is easily detected by immunostaining using the neuropeptide Y-Y1 receptor markers [2]. The incidence of peripheral neuropathy

is about 2.4% globally, and the prevalence tends to triple when considering older populations [4]. Even though diabetes mellitus remains the leading cause of peripheral neuropathy, the rising incidence of malignancies around the world makes chemotherapy-induced PN one of the leading causes as well. It is postulated that the incidence estimate from the latter is around 68% (95% CI, 57.7-78.4%) at any time after chemotherapeutic therapy is initiated [5]. Apart from chemotherapy-induced PN, a lot of other medications have been found to be culprits as well. Although many overlapping features have been investigated, it is very likely that the pathophysiology, clinical aspects and eventually management, differ substantively. Anesthetics, antibiotics, anti-arrhythmatics and antipsychotics along with others constitute the major causes of medication induced PN. A lot of studies have been done to assess the optimal workup plan for drug induced peripheral neuropathy [6, 7]. The major drugs discussed in this manuscript are included in Table 1.

Table 1. Drugs inducing peripheral neuropathy.

Class	Drugs
Chemotherapeutic medications	Taxanes, Vincristine, Platinum drugs, Proteasome inhibitors, Epothilones, Eribulin, Brentuximab vedotin, Suramin, Leflunomide, Gold salts, Chloroquine
Antimicrobials	Chloramphenicol, Dapsone, Ethambutol, Fluoroquinolones, Nitrofurantoin, Metronidazole Isoniazid
Cardiovascular agents	Statins, Hydralazine, Procainamide
Miscellaneous agents	Nitrous oxide, Disulfiram, Colchicine, Heroin, Lithium, Phenytoin

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2. CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY

2.1. Taxanes (Paclitaxel and Docetaxel)

Taxanes, including Paclitaxel, a natural compound, and Docetaxel, a semisynthetic compound, constitute a class of antineoplastic drugs effective against many solid tumors [8]. They have been approved by the FDA for the treatment of ovarian cancer, breast cancer, prostate cancer and non-small cell lung cancer [9]. Taxanes exert their antineoplastic effects by disrupting the normal cycling of microtubule depolymerization and repolymerization, thus interfering with mitotic spindle formation in tumor cells, resulting in cell death [9]. Peripheral neuropathy is an important dose-limiting side effect of treatment with taxanes, particularly paclitaxel, that is more commonly associated with chemotherapy-induced PN, despite being slightly less potent than docetaxel [10, 11]. Taxane-induced PN develops at threshold doses close to standard doses used in many chemotherapeutic regimens at approximately 300 mg/m² for paclitaxel, and 100 mg/m² for docetaxel [12-14]. Higher single, as well as higher cumulative doses, have been reported to increase the susceptibility of patients treated with taxanes to develop neuropathy and more severe symptoms [15-17]. Furthermore, pre-existing peripheral neuropathy and concomitant treatment with other neurotoxic agents are predisposing factors for the risk of developing chemotherapy-induced PN [18]. Neuropathy caused by taxanes mostly affects small-diameter sensory fibers with a predominance of sensory symptoms, including paresthesias, dysesthesias, numbness, altered proprioception and loss of dexterity, predominantly in the toes and fingers (stocking-and-glove distribution) [19]. Motor manifestations including distal weakness, muscle cramps and muscle aches, in addition to autonomic effects such as arrhythmias and orthostatic hypotension, are less common and occur at high doses [20-22]. Symptoms are dose-dependent and tend to improve after completion of treatment; however, some patients can continue experiencing symptoms for 1 to 3 years after stopping the treatment and others can have lifelong manifestations [23]. Many pathophysiological mechanisms underlying taxanes-induced peripheral neuropathy have been proposed. Taxanes cause microtubule aggregation and bundling leading to disruption of cell stability and impairment of axonal transport of synaptic vesicles [24-26]. These processes result in the degeneration of distal nerve segments (Wallerian degeneration) [27]. Taxane-induced mitochondrial damage contributes to the production of Reactive Oxygen Species (ROS), such as hydroxyl radicals, peroxide, superoxide and single oxygen, leading to activation of apoptotic processes, disruption of cell structure and demyelination of peripheral nerves [28]. Taxane-induced dysregulation of intracellular Ca²⁺ homeostasis is another mechanism contributing to the development of chemotherapy induced PN [29]. It has also been suggested that taxanes modify the expression and function of Na⁺, K⁺ and TRP ion channels, which results in the hyperexcitability of peripheral neurons [30]. In addition, taxanes cause an increase in the production of pro-inflammatory cytokines (TNF alpha and IL-1 beta) and a decrease in an-

ti-inflammatory cytokines (IL-4 and IL-10) [31, 32]. Consequently, this results in the recruitment and activation of immune cells, and the development of neuroinflammation [33]. These processes have been shown to play a role in the pathogenesis of chemotherapy-induced PN. Treatment of taxane-induced peripheral neuropathy aims to relieve the burden of neurologic manifestations, including neuropathic pain, numbness and tingling. Topical analgesics, antidepressants, and anticonvulsants are recommended by physicians despite no evidence regarding their effectiveness has been reported in the literature [34, 35]. Most robust data for treatment of Taxane-Induced Peripheral Neuropathy (TIPN) has emerged from a large randomized, double-blind, placebo-controlled phase III trial, which enrolled patients with average chemotherapy-induced pain, after paclitaxel, other taxane or oxaliplatin treatment. Patients who received 60mg/daily of duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, reported a decrease in average pain of 1.06 (95% CI, 0.72-1.40) vs. 0.34 (95% CI, 0.01-0.66) among patients who received placebo for 5 weeks [36]. Intriguingly, results from the exploratory subgroup analysis of the study suggested that duloxetine response rate was better in platinum-induced neuropathic pain, compared to painful TIPN. In addition, duloxetine should be carefully administered in breast cancer patients with TIPN receiving tamoxifen, since duloxetine-induced CYP P450 2D6 enzyme inhibition could prevent the correct conversion of tamoxifen to its active metabolite, endoxifen [36].

Nanoparticle albumin-based paclitaxel (nab-paclitaxel; Abraxane[®]) is a solvent-free formulation of paclitaxel that was first approved by the FDA in 2005 for the treatment of metastatic breast cancer [37]. This Cremophor-EL free formulation of paclitaxel binds albumin to circumvent the requirements for solvents with standard paclitaxel and to avoid solvent-related toxicities, particularly neutropenia [38].

Compared with standard paclitaxel, this solvent-free formulation has several practical advantages such as the decreased risk of hypersensitivity reactions resulting in no need for premedication, shorter infusion period (30 min) and without the need for intravenous tubing [39]. This albumin-bound paclitaxel is a nanoparticle with a small diameter that favors intracellular uptake, transportability to tumor and antineoplastic activity [40]. The proposed mechanism of drug delivery and concentration into tumor cells involves albumin binding to SPARC (secreted protein, acidic and rich in cysteine). SPARC is an extracellular matrix glycoprotein that has been shown to be overexpressed in multiple tumours, and associated with tumour metastasis, including deadhesion, migration and angiogenesis [41, 42]. It has been suggested that SPARC may contribute to albumin concentration in neoplastic cells [43]. Recent evidence in an MX-1 mammary tumour model revealed that the intratumor concentration of nab-paclitaxel was 33%, higher than that of Cremophor EL (CrEL) solvent-based paclitaxel [44]. Other data suggest that albumin initiates endothelial cell transcytosis of paclitaxel-bound albumin by binding to a cell surface, 60K-Da glycoprotein (gp60) receptor, mediating drug delivery and concentration in tumor cells [45].

A randomized phase III trial conducted by Gradishar *et al.* demonstrated that nab-paclitaxel has a higher administration dose of 260 mg/m² compared with solvent-based paclitaxel at 175 mg/m² in a 3-weekly schedule [46]. In this phase III trial, the response rates in patients treated with nab-paclitaxel were shown to be greater than that of the solvent-based formulation of paclitaxel in patients with metastatic breast cancer, demonstrating a better therapeutic index [3]. However, in this trial, patients treated with nab-paclitaxel had a higher rate of sensory neuropathy [46]. Peng *et al.* conducted a meta-analysis to calculate the incidence and Relative Risk (RR) of peripheral neuropathy in cancer patients treated with nab-paclitaxel [47]. The results indicated that the overall incidence of all-grade peripheral neuropathy was 51.0% (95% CI: 45.1-57.6%), and that of high-grade peripheral neuropathy was 12.4% (9.8-15.7%). The RRs of peripheral neuropathy of nab-paclitaxel compared to taxanes (paclitaxel and docetaxel) were not increased. However, the study did not take into account the influence of other chemotherapy agents administered simultaneously, and other concomitant diseases such as diabetes [47].

Another meta-analysis conducted by Guo *et al.* indicates that the incidence and severity of peripheral neuropathy induced by nab-paclitaxel are higher than solvent-based paclitaxel among cancer patients who received monotherapy [48]. The mechanisms of higher incidence and severity induced by nab-paclitaxel are still unclear. The doses, schedule and cycles, as well as the ethnicity and cancer types of patients, are variable and could influence the comparison [48]. As with standard paclitaxel, albumin-bound paclitaxel elicits sensory neuropathy in a dose- and schedule-dependent fashion [48, 49], that is cumulative, additive with platinum treatment [49]. In addition, repeated administration of nab-paclitaxel dose-dependently induced both mechanical and cold allodynia in rats, and these effects on pain behaviors tended to be stronger than that of standard paclitaxel at the doses used clinically [50].

Current evidence suggests that more attention should be paid to peripheral neuropathy when administering nab-paclitaxel in clinical settings.

2.2. Platinum Drugs (Cisplatin, Carboplatin and Oxaliplatin)

Platinum drugs, including cisplatin, carboplatin and oxaliplatin, have become an important part of the combination chemotherapy regimens that have a broad spectrum of activity against several solid tumors [51]. Cisplatin is the first agent of platinum drugs used in many kinds of solid tumors, including lung, ovary, testis, bladder, head and neck, and endometrium [52, 53]. Since cisplatin was discovered in the mid-1960s, many other second and third generations of platinum have emerged in view of considerable side effects, especially neurotoxicity [54]. Carboplatin, a second-generation platinum compound, has been developed to treat ovarian, non-small cell lung and refractory testicular cancers [55]. Oxaliplatin, a third-generation platinum analog, is used in combination with folic acid and 5-fluorouracil as a part of

the FOLFOX regimen for first-line and adjuvant colorectal cancer therapy [56]. Despite platinum drugs' favorable anti-tumor properties, concerns of induced neurotoxicity often prevent their administration at their full efficacious doses affecting the quality of life (QOL) [57, 58]. The intracellular concentration of platinum-based compounds is maintained *via* many metal transporters, such as the copper transporters CRT1 which mediate active drug uptake and entry into the tumor and normal cells [59, 60]. Platinum drugs can be excreted *via* copper-transporting ATPases that mediate efflux, such as ATP7A and ATP7B [61]. Platinum-based compounds interfere with tumor cell proliferation by mediating the intracellular formation of DNA-platinum adducts *via* a hydrolysis process, resulting in inter-strand crosslinks, intra-strand crosslinks and/or DNA-protein crosslinks with platinum, affecting DNA synthesis in cancer cells, and subsequent apoptosis of dividing tumor cells [62-64]. A number of pathophysiological mechanisms have been proposed to explain cisplatin-mediated neurotoxicity including the loss of peripheral sensory neurons, changes in cell signaling cascades, altered Ca²⁺ homeostasis and mitochondrial function, oxidative stress and activation of apoptotic pathways as a result of DNA platination [65]. Dorsal Root Ganglion (DRG) is the main target of platinum drugs. Platinum-DNA adducts accumulate in DRG and the extent of subsequent DNA crosslinks in DRG neurons correlates with the degree of neurotoxicity [66]. Platinum adducts produced by cisplatin in DRG are approximately three times higher, compared with oxaliplatin, and concordantly cisplatin has a higher neurotoxicity profile than oxaliplatin [67, 68]. The most accepted mechanism contributing to the development of oxaliplatin-induced neurotoxicity is the accumulation of oxaliplatin in DRG resulting in decreased cellular metabolism and axoplasmic transport, ultimately leading to symmetrical, axonal, and sensory distal neuropathy [69]. Carboplatin has the least neurotoxic profile compared with that of cisplatin and oxaliplatin. Nevertheless, carboplatin-induced neurotoxicity appears later on, after the administration of high-dose levels or in combination with other cytotoxic agents [70-72]. In an experiment performed *in vitro*, exposing rat sensory neurons in culture to the three platinum drugs, cisplatin, oxaliplatin or carboplatin, caused a concentration-dependent increase in apoptosis and cell death, although carboplatin required a 10-fold higher drug concentration than cisplatin to result in a similar degree of cytotoxic effect [73]. Platinum compounds affect predominantly large-diameter sensory nerve fibers, resulting in symmetrical glove and stocking type of sensory loss, and many other sensory symptoms, including numbness, tingling, pain and burning sensation [74]. Carboplatin-induced PN affects only 4-6% of patients, less frequent than that observed with cisplatin or oxaliplatin [75, 76]. Factors predisposing to carboplatin-induced neurotoxicity include age above 65 years and pretreatment with other neurotoxic agents [68, 77]. PN is one of the most important dose-limiting side effects associated with cisplatin [78]. Generally, cisplatin induced neurotoxicity is delayed and develops after cumulative doses higher than 350 mg/m², with approximately 92% of patients developing neurotoxic symptoms at

cumulative doses of 500-600 mg/m² of cisplatin [79-81]. Signs and symptoms of peripheral neurotoxicity involve the upper and lower limbs, and include mixed sensory and motor defects, including loss of vibration sense and position sense, tingling, paresthesia, weakness, tremor and loss of taste [79, 80, 82]. After discontinuation of treatment, cisplatin induced neuropathy symptoms may persist, or show continued worsening over several months, a phenomenon called "coasting" [83]. The neurotoxic effects of oxaliplatin can present as two forms: an acute, transient PN that occurs during the administration of oxaliplatin or within few hours of drug infusion and is characterized by dysesthesias and paresthesia in the extremities and the perioral region. These symptoms are often exacerbated by cold exposure and are a key feature of oxaliplatin-induced allodynia [84]. Acute oxaliplatin induced neuropathy generally subsides between treatment cycles [85]. The second pattern of neurotoxicity is the chronic cumulative sensory neuropathy which causes more persistent clinical impairments [57]. Approximately, 70% of patients who receive oxaliplatin treatment develop chronic PN with the development of the condition usually occurring at cumulative doses exceeding 540 mg/m², and the risk appears to be lower if oxaliplatin is administered at a dose of 85 mg/m² every 2 weeks rather than 130 mg/m² every 3 weeks [84, 86-88]. In addition, motor symptoms consist mainly of fasciculations, tetanic spasms, and prolonged muscular contractions [89]. Furthermore, patients can develop Lhermitte's sign, which is a shock-like electric sensation experienced with neck flexion. This phenomenon indicates the involvement of the centripetal branch of the sensory pathway within the CNS, notably the spinal cord [90]. Genetic risk factors behind the development of oxaliplatin neurotoxicity include variations in genes, such as glutathione-S-transferase genes P1 [GSTP1] and glutathione-S-transferase genes M1 [GSTM1]. Other risk factors include the cumulative dose, low body weight, a body-surface area >2.0 m², young age, and persistent neuropathy in a past cycle [89, 91]. Platinum-induced neurotoxicity can be assessed using self-reporting questionnaires developed by the United States National Cancer Institute and European Organization for Research and Treatment of Cancer (EORTC), which have been recommended for grading previous or new neuropathy [92, 93]. These questionnaires evaluate the occurrence, frequency and degree of distress of neuropathic symptoms and their impact on patient's quality of life [94]. Despite the reliability of these assessment tools, there are concerns of lack of congruence between subjective patient perception and objective tools, especially in intermediate grades, which accentuates the importance of a more effective and standardized method [92, 95]. Nerve biopsies and neurophysiologic assessments are useful for determining nerve impairments [96]. Among neurophysiological techniques, nerve conduction velocity studies and electromyography remain the gold standard technique for detecting the location and degree of platinum induced neuropathy [14, 54]. Electromyography (EMG) is a widely available diagnostic technique that can efficiently detect oxaliplatin-induced motor nerve hyperexcitability on days 2 to 4 post-treatment [97]. Furthermore, the

threshold tracking technique allows the prediction of sensory nerve pathologies prior to the development of clinical manifestations [98].

2.3. Vinca Alkaloids (Vincristine and Vinblastine)

Vincristine (VCR) is a chemotherapy drug that belongs to the family of vinca alkaloids, which also includes vinblastine and vindesine and has been gradually used since 1963 [99]. VCR is an important antineoplastic drug for chemotherapeutic treatment of several solid tumors and hematologic malignancies, including breast cancer, non-Hodgkin lymphoma and leukemia [100]. VCR is commonly used in the induction and consolidation phases during the treatment of Acute Lymphoblastic Leukemia (ALL), and it is a component of many different chemotherapy regimens (*e.g.*, MOPP, COPP and BEACOPP regimen for therapy of Hodgkin's disease) [56, 99]. VCR exerts its antineoplastic effect by binding to the β -subunit of tubulin, inhibiting its polymerization and incorporation into microtubules. Microtubules are cytoskeletal proteins involved in the regulation of cell shape, mitosis, cell division and cellular transport, and their proper function depends on the balance between aggregation and disaggregation of tubulin subunits. Thus, VCN induced inhibition of tubulin polymerization stops microtubule formation during mitosis, leading to mitotic arrest and cell death [101]. The dose-limiting side effect of VCN is peripheral sensory and motor neurotoxicity, which could ultimately lead to dose reduction, treatment substitution or discontinuation [102]. The antimitotic drug interferes with microtubules, therefore blocking vesicle-mediated axoplasmic transport in nerves, leading to axonopathy and subsequent neuropathy [103]. The mechanisms leading to VCN induced PN include disruption of Ca homeostasis resulting in altered mitochondrial function, activation of the innate and adaptive immune system and subsequent neuroinflammation, leading to membrane remodeling of neuronal cells, altered excitability of peripheral neurons and ultimately loss of large, myelinated fibers [104-106]. Vincristine Induced Peripheral Neuropathy (VIPN) spans a broad spectrum of dysfunction that fall into sensory, motor and autonomic components, with tendon reflexes, vibration sensitivity and strength most affected in the first year of treatment [107]. VCN induced sensory neuropathy is characterized by paresthesia in the form of numbness, tingling and pricking, and neuropathic pain in the upper and lower extremities. Sensory dysfunction also includes loss of sensory discrimination, specifically an inability to detect light touch, pinprick sensations or vibrations and temperature recognition [108-110]. VCN induced motor neuropathy is characterized by weakness in the upper and lower extremities, and wrist or foot drop due to impaired dorsiflexion that arises from damage to peripheral nerves. In addition, patients receiving VCN experience walking difficulties, muscle cramps, and weakened Deep Tendon Reflexes (DTRs) [111]. Typical symptoms of autonomic neuropathy are constipation, urinary retention, orthostatic hypotension, ileus and incontinence [109, 112].

2.4. Proteasome Inhibitors (Bortezomib and Carfilzomib)

The Ubiquitin Proteasome System (UPS) is the mechanism that maintains the homeostatic level of many intracellular proteins. It is the major extralysosomal protein degradation pathway in eukaryotic cells [113]. Interruption of UPS activity can induce an apoptotic cascade and the accumulation of misfolded regulatory proteins [114]. Proteasome inhibitors, including Bortezomib and Carfilzomib, have become an important part of chemotherapeutic regimens used to treat lymphomas and Multiple Myeloma (MM), a malignant plasma-cell disorder that affects around five in 100,000 people each year and accounts for roughly 10% of all hematological malignancies [115]. Bortezomib (BZT), a dipeptide boronic acid analog, selectively inhibits the $\beta 5$ and $\beta 1$ subunits of the 20S proteasome core in the 26S proteasome complex [116]. This leads to the accumulation of misfolded proteins in the endoplasmic reticulum and cytosol of cells causing ER overload, generation of excess oxygen species and disruption of intracellular proteins, thereby leading to apoptosis and cell death [117]. The hallmark of bortezomib action is the inhibition of the NF- κ B pathway, which plays a critical role in the pathogenesis of MM [117]. Bortezomib monotherapy was approved by the US Food and Drug Administration (FDA) for the treatment of mantle cell lymphoma in 2006 and of MM in 2008 [118]. PN is a significant dose-limiting toxicity of Bortezomib which develops in up to 50% of BTZ-treated MM patients [119, 120]. Since Bortezomib is the mostly used proteasome inhibitor clinically, different hypotheses have been proposed regarding the pathophysiological mechanisms underlying Bortezomib-Induced Peripheral Neuropathy (BIPN). Intracellular dysregulation of Ca^{2+} homeostasis, leading to mitochondrial calcium level increase, is a critical regulator of bortezomib-induced toxicity. Increased calcium levels can lead to caspase activation, thus causing apoptosis. Furthermore, it has been reported that mitochondrial dysfunction may lead to oxidative stress and subsequent neuronal damage [121]. Bortezomib-mediated inhibition of NF- κ B, a pathway relevant in MM pathogenesis, has been proposed as another important mechanism [122]. NF- κ B inhibition could be responsible for a reduction in nerve growth factor and brain-derived growth factor (BDNF), thus leading to altered neuronal survival [123, 124]. It has also been suggested that Bortezomib is involved in increased tubulin polymerization in both dorsal root ganglia (DRG) and sciatic nerves, as demonstrated in a BIPN rat model [125, 126]. DRG appears to be the main target of Bortezomib as confirmed in Casafont *et al.*'s observation, which underlined the accumulation of ubiquitinated proteins in DRG neurons of BTZ-treated rats [127]. In rat models, bortezomib caused damage in satellite cells of dorsal root ganglia (DRG) and induced painful non-myelinated axonopathy [128, 129]. An intriguing hypothesis is related to the role of neuroinflammation as a trigger for Bortezomib induced PN development [130]. Inflammation, mitochondrial changes, cytoskeletal damage, and oxidative stress are the pathways whereby Bortezomib is thought to develop neuropathic pain [131]. Carfilzomib is a second-generation protea-

some inhibitor that has been proven to have less neurotoxicity in animal models when compared to Bortezomib. This has been explained by its rapid clearance potential, and irreversible binding of carfilzomib to proteasomes in hepatocytes and red blood cells, thus restricting its tissue distribution and enabling fewer molecules of carfilzomib to reach DRG [132, 133]. Proteasome inhibitors induced PN is characteristically dose-dependent, length-dependent, mixed small and large fiber axonal sensory neuropathy and may resolve within weeks of discontinuation. Less commonly, a demyelinating neuropathy with marked weakness is reported [134, 135]. Symptoms and signs of BIPN are predominantly sensory characterized by distal sensory loss of all modalities in the lower more than in the upper limbs, suppression of DTRs in proportion to sensory loss and changes in proprioception [136]. The cardinal symptom of BIPN is moderate to severe neuropathic pain, at distal parts of extremities, mainly fingertips and toes or soles [137]. Numbness and paresthesias affecting feet and hands, predominantly symmetric, are frequent complaints [138]. Motor fibers are usually spared, however, severely affected patients may develop muscle cramps, muscle atrophy, or loss of strength in distal muscles [138]. Autonomic neuropathy also characterizes BIPN and is associated with symptoms, including suppressed heart rate variability, orthostatic hypotension and delayed gastric emptying [139]. Other symptoms, such as diarrhea, ileus, impotence and urinary disturbances, have also been reported [140]. Genetic risk factors have been postulated to increase susceptibility of patients treated with bortezomib to develop neuropathy. One study proposed certain polymorphisms in genes related with immune function, Schwann cell junction and neuron function were related to the onset of the neuropathy [141]. Another genetic study described a link between an increase in inflammatory genes and major incidence of neurological pathologies [142]. Furthermore, pre-existing PN is a predisposing risk factor for developing BIPN [57, 142-145]. Interestingly, a study reported male-related higher susceptibility to BIPN [145]. Recently, subcutaneous injection of bortezomib has been shown to significantly reduce the incidence of neuropathy without reduction in therapeutic efficacy [146]. Since BIPN is dose-related and cumulative up to a bortezomib dose of approximately 42 - 45 mg/m², an early and active dose modification is recommended for an excellent efficacy and an improved safety profile [117, 147]. Assessment of Bortezomib induced toxicity is based primarily on different approaches of clinical examination, summarized by several comprehensive neurotoxicity grading scales [148]. The most widely used grading systems for evaluating the extent of peripheral nerve damage are the National Cancer Institute-Common Toxicity Criteria [NCI-CTC], Eastern Cooperative Oncology Group criteria, Ajani, and the World Health Organization criteria [145, 149-151].

2.5. Epothilones (Ixabepilone and Sagopilone)

Epothilones are anti-tubulin agents derived from the myxobacterium *Sorangium cellulosum*, divided into two major fermentation products: Epothilone A and Epothilone B [152, 153]. Epothilones are represented mainly by Ixabepi-

lone, a second-generation semisynthetic analogue of Epothilone B, used in the treatment of metastatic breast cancer [154]. Sagopilone is a fully synthetic third generation Epothilone B derivative, which is considered a good therapeutic option against breast cancer, non-small cell lung cancer, cholangiocarcinoma, melanoma and adrenal carcinoma [155, 156]. Epothilones are relatively new antineoplastic drugs that bind preferentially to the beta III tubulin, acting as tubulin destabilizers, and consequently, preventing the division of cancer cells [28]. Despite epothilones being a good therapeutic option for many neoplasms, the emergence of neuropathic symptoms continues to be a concern. Epothilone-induced PN is primarily an axonal, reversible, dose-dependent, sensory distal neuropathy, usually manifesting as paresthesia, dysesthesia, numbness and/or burning neuropathic pain in a stocking-glove distribution [157]. Motor symptoms are less frequent but possible and can manifest as mild muscle weakness such as difficulty in climbing stairs. Autonomic manifestation is very rare and is experienced in less than 1% of patients. The symptoms are dose-dependent and tend to improve after stopping the treatment [158]. The mechanisms underlying epothilone-induced neuropathy include microtubule disruption, which impairs axonal transport, and leads to degeneration of distal nerve segments (Wallerian degeneration). Furthermore, epothilones are able to damage mitochondrial DNA transcription, leading to an increased production of Reactive Oxygen Species (ROS), resulting in damage of proteins and lipids within neurons, consequently leading to altered excitability of peripheral neurons. Moreover, the ROS induced activation of T-lymphocytes and monocytes leads to the release of proinflammatory cytokines and the development of neuroinflammation [158].

2.6. Halichondris (Eribulin)

Eribulin mesylate is an anti-tubulin agent belonging to the class of halichondrins, a synthetic derivative from the Japanese marine sponge, *Halichondria okadai* [159]. Eribulin mesylate is a chemotherapeutic agent that inhibits microtubular growth *via* tubular aggregation and is primarily used in metastatic breast cancer cases not responsive to first-line therapies [160]. Eribulin has promising therapeutic efficacy against a wide range of cancers (lung, bladder, cervical, esophageal, and head and neck cancer), and survival has shown to be significantly improved in locally advanced or metastatic breast cancer [161, 162]. Despite its antineoplastic effect, Eribulin has the potential for neurotoxicity. In animal models, Eribulin has been shown to induce microtubule depolymerization, leading to disruption of axonal transport and subsequent neuropathy [25, 163]. Furthermore, Eribulin disrupts mitotic spindle formation due to non-functional aggregates of tubulin, halting metaphase/anaphase of cell division [164, 165]. Eribulin is associated with sensorimotor, mainly sensory, polyneuropathy. Meta-analysis of a large subset of patients revealed that the majority develops a low- to moderate neuropathy [161]. Factors predisposing to the development of PN are many, including age, underlying malignancy, cumulative dose, single-dose intensity, a combi-

nation of neurotoxic agents, duration of treatment, genetic susceptibility, previous chemotherapy regimen, and coexisting neuropathy [166, 167].

2.7. Anti-CD-30, An Anti-Microtubule (Brentuximab vedotin)

Brentuximab vedotin (BV) is an antibody-drug conjugate composed of a specific antibody targeting CD30 and the antimicrotubule drug monomethyl auristatin E (MMAE) connected by a protease-cleavable linker [168]. It has demonstrated therapeutic efficacy against many CD 30-expressing lymphomas, including Hodgkin lymphoma, systemic anaplastic large cell lymphoma and CD-30 positive peripheral T-cell lymphoma [169, 170]. BV was approved in August 2011 by the U.S. FDA for the treatment of patients with Hodgkin lymphoma relapsing after autologous stem cell transplantation (auto-SCT) or after the failure of at least two prior multi-drug chemotherapy regimens in patients with Hodgkin lymphoma ineligible for auto-SCT, and for the treatment of systemic anaplastic large cell lymphoma (ALCL) after the failure of at least one multi-agent chemotherapy regimen [171]. CD30 is a membrane glycoprotein that belongs to the TNF receptor (TNFR) superfamily, which comprises 29 members, including Fas and TNFR1 [172, 173]. BV binds to the extracellular domain of the CD30 receptor and is internalized by clathrin-mediated endocytosis, and subsequently travels to the lysosome. Upon exposure to proteolytic lysosomal enzymes, the linker peptide is cleaved, and MMAE molecules are released into the intracellular space [174]. The binding of MMAE to tubulin disrupts microtubule polymerization, leading to induction of G2/M-phase cell cycle arrest and apoptosis in CD30-expressing lymphoma cells. Antineoplastic effect by BV may also be mediated by antibody-dependent cellular phagocytosis (ADCP) or *via* direct effects on tumor cell signaling [175]. In addition, a small fraction of MMAE diffuses out of the CD30-positive cells into their surrounding microenvironment, allowing it to exert a bystander effect, as an important, possibly essential mechanism of killing surrounding cells, independently of whether CD30 is expressed [176]. Although BV has proven to be a highly promising drug for patients with CD30-positive lymphoma, PN is a typical side effect typically manifesting predominantly as sensory symptoms [168]. In a series of detailed clinical assessments in 10 patients on BV treatment, after a median of four cycles, the majority of patients (90%) developed new or progressive symptoms during BV treatment. The notable sensory symptoms were numbness (70%), paresthesias (70%), tingling (60%), and burning pain (40%), associated with a predominantly axonal neuropathy. Further, 60% of patients reported neuropathic pain [177]. Another detailed study in 36 patients demonstrated a high proportion of patients with grade 2 or greater neuropathy (50%) with predominantly length-dependent axonal damage on nerve conduction studies [178]. Moreover, 50% of patients reported motor symptoms, characterized by mild distal weakness in the upper and lower limbs [177]. BV-induced PN is cumulative and dose-dependent, with pharmacokinetic analyses identified possible PN associated with BV expo-

sure, suggesting that dose modification could be a method of prevention [179]. In the ECHELON-1 trial, PN occurred in 67% of Hodgkin lymphoma patients treated with vinblastine-containing regimens plus BV, demonstrating an additive burden of PN when BV is administered with other neurotoxic agents [169]. Despite the neurotoxic effects of microtubule targeting agents, the pathophysiological mechanisms underlying BV-induced PN remain unclear [177]. Given the severity of BV associated neuropathy, a sural nerve biopsy was performed in several patients, which showed features including active axonal neuropathy with decreased density of myelinated fibers of all calibers, ongoing wallerian-like degeneration and sporadic small clusters of regenerating fibers, in the absence of cellular inflammation and CD30 expression [178, 180]. It has been postulated that there may be an effect of free MMAE molecules.

2.8. Tryptan Derivative (Suramin)

Suramin is a promising experimental chemotherapeutic agent with potential use in the treatment of hormone-refractory or metastatic prostate cancer [7]. It was first synthesized in 1916 as a colorless derivative of tryptan dyes used as an antiparasitic agent against African trypanosomiasis, and later found to be a potent reverse transcriptase inhibitor with limited beneficial effect against the HIV virus [181-183]. During trials in HIV patients, Suramin was found to have ancillary benefits against Kaposi sarcoma and lymphoma [7]. The drug shows a good therapeutic profile in solid tumors, including prostate and colon cancer, as well as lymphoma; however, toxic neuropathy as a side effect is a limiting factor for its approval in the United States [7]. PN is a significant dose-limiting toxicity which occurs in 40-79% of suramin-treated patients [184-186]. Suramin injected in rats models induces a length-, dose-, and time-dependent axonal sensorimotor polyneuropathy associated with axonal degeneration, atrophy, and accumulation of glycolipid lysosomal inclusions [187]. It induces characteristic lipid storage disease findings on histology and is associated with the inhibition of enzymes involved in sphingolipid degradation [188]. There has been an indication that the neuropathy is dose-dependent. About 40% of patients with plasma peak levels of suramin over 350 $\mu\text{g/ml}$ develop sensorimotor neuropathy. Duration of chemotherapy and cumulative doses also determine the incidence and severity of suramin-induced neuropathy [189]. As suramin is a highly charged molecule and does not normally cross the blood brain barrier, it does not exert its neurotoxic effects on the central nervous system; instead, peripheral system neuropathy is the main problem in human therapy [190]. Suramin-induced PN manifests as a mix of predominantly sensory and motor symptoms, including hypoesthesia, paresthesia, dysesthesia, hypoaesthesia or pallesthesia [186, 191]. Neuropathy can be severe, and some patients can have clinical courses mimicking subacute Guillain-Barré Syndrome (GBS) with flaccid paralysis [189]. Suramin-treated patients have acute signs of demyelination and elevated cerebrospinal fluid protein, resembling GBS [7]. Many pathomechanisms underlying suramin induced PN have been described. In suramin-treated

neurons, suramin resulted in accumulation of GM1 gangliosides and ceramide, an important mediator of apoptosis, raising the suggestion of suramin mediated neurotoxicity *via* programmed cell death [191]. Another mechanism seems to be the inhibition of lysosomal enzymes by suramin, resulting in gangliosidosis with intracellular lamellar inclusion bodies in neurons and Schwann cells [192, 193]. Furthermore, some studies describe that suramin leads to inhibition of P2 receptors leading to disturbance of intracellular Ca^{2+} homeostasis in intact peripheral nerves and consecutively resulting in cell damage [187, 189]. Calcium influx into DRGN appears to be an underlying pathomechanism of suramin neurotoxicity, as Nimodipine, an L-Type Voltage-Gated Calcium Channel (VGCC) inhibitor, showed limited neuroprotective effects [194]. Suramin has also shown inhibition of DNA polymerase and several growth factors, including nerve growth factor (NGF), and it decreases the binding affinity of suramin to the nerve growth factor receptor, suggesting an intriguing neurotoxic mechanism [191, 195].

2.9. DMARD (Leflunomide)

Leflunomide, a new disease-modifying drug (DMARD) used in the treatment of rheumatoid arthritis (RA), was approved in the US in September 1998 and in Australia in September 1999 [196, 197]. Leflunomide is an isoxazole derivative that is rapidly converted in the plasma to its active metabolite A77 1726, which has immunosuppressive properties [198]. RA is characterized by the rapid proliferation of CD4+ T cells, requiring an increased pyrimidine nucleotide pool. Leflunomide disrupts the synthesis of the *de novo* pyrimidine ribonucleotide uridine monophosphate by reversibly binding dihydroorotate dehydrogenase, leading to a reduction in DNA synthesis and T-cell clonal expansion [199]. Consequently, Leflunomide reduces inflammation and prevents joint manifestations of rheumatoid arthritis, notably cartilage erosion and joint destruction [198, 200]. The safety profile of this drug has been assessed in phase II and phase III clinical studies involving several thousand patients [201, 202]. Leflunomide has been shown to have safety and efficacy maintained after 2 years of treatment [203]. However, earlier pre-release studies of this drug showed a 3-4% incidence in sensory symptoms but no documented PN [204]. Since the release of Leflunomide, around 80 cases have been reported to the US FDA concerning induced neuropathy [205]. In addition, 14 cases of PN in RA patients treated with Leflunomide have been reported to the regional pharmacovigilance center in Bordeaux [206]. Carulli and Davies were the first researchers to raise the question of leflunomide-induced PN in 2002 and postulated that neurological vasculitis could be the underlying mechanism of induced neuropathy [207]. Nevertheless, this hypothesis could not be investigated in the absence of a neuromuscular biopsy. In support of this hypothesis, two cases in the case series were found to have non-specific vasculitis diagnosed by neuromuscular biopsy when looking for the etiology of the neuropathy [206]. Bonnel and Graham performed a study on 80 patients with PN, treated with leflunomide. Their findings emphasized that no relationship between age, sex or dose

and the time to onset of neuropathy or the degree of reversibility, could be established. However, better prognosis and even complete recovery were noted in patients who discontinued leflunomide treatment within 30 days of the symptoms [205]. The cases reported by Bonnel and Graham were typically axonal, sensory or sensorimotor polyneuropathy [205]. Around 1 to 18% of patients with RA reported paresthesia with normal nerve conduction studies (NCS) [208]. The clinical manifestations of peripheral nervous system involvement include most commonly compression neuropathy and mild axonal sensory neuropathy. Multiple mononeuritis and severe distal sensorimotor neuropathy usually occur in the severe form of RA [209].

2.10. Gold Salts

Gold neuropathy is a rare complication of gold therapy in RA patients [210]. The first survey of the case reports mentioned in the literature was found in French journals by Leshner in 1936 [211]. Five years later, Sundelin reported 107 patients out of 964 treated with gold therapy, who developed neurologic complications, including gold encephalopathy [212]. Interestingly, gold has been found to localize in the nervous system in animal models [193, 213]. Another study on the distribution of an obesity-producing dosage of gold in mice showed localization of gold in the dienkephalon [213]. In three published reports, gold-induced neuropathy manifests as weakness of the hands and wrists, loss of sensation in a glove and stocking distribution, and hyperesthesia in the palmar finger pads [193]. Endtz classifies gold-induced neuropathy into three categories: the first one is painful neuropathy, sometimes accompanied by insomnia and anxiety; the second constitutes peripheral motor neuropathy, including Guillain-Barre-like syndrome; and the third category is encephalopathy, which manifests as depression, delirium, or exogenous psychosis [214]. Autonomic manifestations include myokymia (a typical finding of gold neurotoxicity), tachycardia, hyperhidrosis, hypertension in the recumbent position and postural hypotension [215]. The pathomechanism underlying gold induced neuropathy remains unclear, however nerve biopsies performed in three patients with RA with no evidence of vasculitis were consistent with axonal degeneration and loss of thickness of myelinated fibers [210, 216].

2.11. Quinolone (Chloroquine)

Chloroquine is one of the quinolone derivatives that were introduced for the first time as antimalarials during and after World War II [210]. Chloroquine is widely used in clinical practice for the treatment and prophylaxis of malaria and in the treatment of mild and moderately severe stages of connective tissue disorders, such as RA and Systemic Lupus Erythematosus (SLE) [217]. The treatment of such conditions often requires prolonged administration of large and frequent doses and is associated with neurological side effects [218]. Patients treated with chloroquine for months or years developed proximal weakness and loss of tendon reflexes of the lower extremities [219]. The neuropathy later involves the upper limb and facial muscles (weak mastication, double vision) [220-222].

Electrophysiological studies have demonstrated the concurrence of myopathic and neuropathic changes [223]. Tegnér *et al.* conducted a study on four patients treated with chloroquine; three of them were treated for connective tissue disease, while one patient used this drug as malaria prophylaxis. Nerve biopsies performed on these patients demonstrated the presence of segmental demyelination and remyelination in all cases with cytoplasmic inclusions noted in Schwann cells. Perineurial calcifications were found in two cases [217]. Curvilinear body formation has also been reported in pericytes surrounding capillaries in the perineurial space of muscle biopsy samples [224-226]. CSF is typically normal in chloroquine-induced polyneuropathy; however, CSF protein can be increased due to increased vascular permeability secondary to inflammatory or immune-mediated neuropathies [220, 221, 227]. The exact mechanism underlying chloroquine induced neuropathy is not clear, but there are studies demonstrating induced inhibition of lysosomal enzymes involved in glycogen or protein metabolism, due to chloroquine-induced increase of the intralysosomal pH [220].

2.12. Other Drugs Associated with CIPN

The following medications are some rare causes of PN. They can be split into three main categories: cell cycle inhibitors, antimetabolites and hormones. Derived from podophyllin, Etoposide (VP16) and Teniposide (VM26) are both spindle and topoisomerase (TOP) inhibitors, and they inhibit TOP II. Irinotecan/topotecan inhibits TOP I. The main function of topoisomerases is to create a single or double-stranded break in the DNA helix to add or remove supercoils. These drugs interfere with DNA damage repair, thus facilitating apoptosis and rarely causing PN [228]. Other medications less commonly associated with PN are Methotrexate, Cytosine arabinoside, Gemcitabine and 5-Fluorouracil. Methotrexate is a folic acid analog that competitively inhibits dihydrofolate reductase, leading to a decrease in deoxythymidine monophosphate synthesis and eventually decreased DNA synthesis. While both 5-Fluorouracil and Cytosine arabinoside function as pyrimidine antagonists, Gemcitabine functions as a deoxycytidine analog [229]. Last, there has been data reported of grade 2 neuropathies occurring in one-third of patients receiving chemotherapy and aromatase therapy. Carpal tunnel syndrome and ulnar entrapment are examples of rare focal neuropathies occurring with aromatase (anastrozole and exemestane) treatment [230, 231].

3. OTHER MEDICATIONS CAUSING PERIPHERAL NEUROPATHY

3.1. Nitrous Oxide (NO)

NO, commonly known as happy gas or laughing gas, is commonly and safely used for minimal sedation through inhalation. It can commonly cause nausea, headache and sleepiness. However, PN has been found to be associated with NO use. It irreversibly oxidizes cobalamin from Co^{+1} to Co^{+3} , preventing the production of methionine and S-adenosylmethionine (SAM).

sylmethionine required for methylation of myelin sheath phospholipid [232]. This leads to a decrease in myelin formation. In addition, it also leads to the incorporation of abnormal fatty acid in the myelin sheath (by an accumulation of methylmalonate and propionate). The end result will be a subacute degeneration of the spinal cord, similar to the findings in B12 deficiency, degeneration of lateral and posterior spinal columns. This results in symmetrical neuropathy affecting the lower extremities at a greater extent more than the upper extremities, starting as paresthesia, decreased vibration and proprioception, evolving to ataxia, weakness, spasticity, fecal and urinary incontinence [232, 233]. Other neurologic findings include irritability, memory loss, and Lhermitte's sign. Patients can also have megaloblastic anemia and subacute combined degeneration syndrome similar to that seen in pernicious anemia. Myelopathy usually occurs 2-6 weeks after the anesthesia in patients with underlying B12 deficiency [233]. Electrophysiologic studies usually reveal axonal sensorimotor neuropathy. Magnetic Resonance Imaging (MRI) of the spinal cord can show a T2-signal hyperintensity of the posterior and less commonly of the lateral columns. The differential diagnosis of hyperintensity on MRI includes infectious/post-infectious myelitis, multiple sclerosis, sarcoidosis, ischemia, lymphoma and other neoplasms, paraneoplastic myelopathy, cervical spondylosis, radiation myelitis, traumatic cord injury, arterial or venous ischemia, vascular malformations of the dura and spinal cord, syringomyelia, metabolic disease (including vitamin E deficiency) and acute transverse myelitis [233]. Serum B12 levels may be low, normal, or high, depending on the extent of nitrous oxide abuse and B12 supplementation. The duration of exposure to the anesthetic is between 1 and 11 hours, with a concentration of 40-66% from the total inspired air; the rest being oxygen. Last, abstinence is the key in treatment. Vitamin B12 supplementation is beneficial only if associated with withdrawal of medication as serum B12 levels do not correlate with treatment response [233].

3.2. Disulfiram

Disulfiram is known for its use as a second-line treatment in chronic alcoholism. It works by inhibiting aldehyde dehydrogenase, an enzyme needed for the metabolism of alcohol. The accumulation of acetaldehyde leads to drowsiness, headache, fatigue, psychosis, and less commonly, PN and neuritis [234]. These reactions are dose-dependent, related to the accumulation of a by-product of disulfiram, carbon disulfide. The neuropathy was described as distal axonopathy due to axonal degeneration [235]. Ansbacher *et al.* reported a case in which a sural nerve biopsy demonstrated neurofilamentous distal axonopathy and cited carbon disulfide as the responsible agent. Clinically, differentiating between disulfiram and alcoholic neuropathy is challenging. Nonetheless, some features help in the distinction [234]. First, disulfiram neuropathy occurs within weeks from starting treatment, compared to the insidious onset of alcohol neuropathy. Second, there appears to be a faster disease progression in disulfiram neuropathy [235]. Third, muscle tenderness, as well as disturbances in sweating of distal limbs,

occur in the former. Both can present with symmetrical distribution, worse distally, with depressed DTRs. Disulfiram neuropathy occurs in chronic alcohol abusers. The frequency with which it occurs is difficult to assess, though one quoted figure is 1:15,000. Neuropathy and electrodiagnostic findings of decreased compound muscle action potential indicating axonopathy after disulfiram therapy can be confidently attributed to disulfiram use, given that patients will have abstained from alcohol during therapy [235]. Another useful study may be to perform a sensory nerve biopsy to determine if small fiber sensory nerves are involved [234, 235].

3.3. Colchicine

The typical presentation of a patient having symptoms from colchicine toxicity would be as follows. A male, 50 to 70 years old, having mild chronic renal insufficiency (creatinine, 1.6 to 4.0 mg/dL [140 to 350 μ mol per liter]) and secondary gout would be treated with 0.6 mg of colchicine taken twice daily. This patient would present because of subacute proximal weakness and he would be found to have a raised serum creatine kinase level (without other evidence of colchicine toxicity) along with a mild coexistent polyneuropathy. The disorder in these patients is usually misdiagnosed as polymyositis because of the elevated creatine kinase activity and a "typical" electromyogram, or as neuropathy related to renal failure or another concurrent illness [236]. Symptoms can develop in the setting of acute overdose or chronic administration in therapeutic doses or during the concomitant use of immunosuppressive drugs or statins. Muscle biopsy specimens are characterized by vacuolar changes. The early diagnosis of colchicine-induced neuromyopathy is important as the reversal of muscle weakness requires termination of colchicine therapy. Colchicine, cyclosporine, and simvastatin are metabolized by cytochrome P450 3A4. Therefore, the concomitant use of these drugs can increase the toxicity of colchicine [236]. Nerve conduction studies typically reveal a reduced amplitude and borderline/slow conduction velocities, which indicates axonal polyneuropathy. Electron microscopy shows subsarcolemmal vacuoles of varying sizes that contain electron-dense lysosomal granules and autophagic material [236]. Electromyography shows myopathic changes, while electron microscopy of muscle biopsy samples shows vacuolar changes (Fig. 1) [237].

On neurological examination, predominantly proximal muscle weakness, which is accompanied by distal areflexia and minor distal sensory loss, would be found. Myopathy generally disappears a few weeks after the cessation of medication, but neuropathy may persist for a long time [238]. Colchicine myoneuropathy is usually misdiagnosed initially, either as probable polymyositis or as uremic neuropathy. Concentric needle electromyography of proximal muscles showed prominent fibrillations and positive sharp waves; motor-unit potentials were excessively polyphasic, brief, and small in amplitude. Such findings are typical of polymyositis and other necrotizing myopathies [236, 238]. Distal muscles also had abnormal spontaneous activity, but motor-unit potentials were long in duration and large in amplitude, indicating chronic denervation and reinnervation

[238]. In all cases examined, nerve-conduction studies using standard techniques showed reduced amplitudes of motor and sensory responses but normal or borderline-slow conduction velocities, indicative of axonal neuropathy [236, 238].

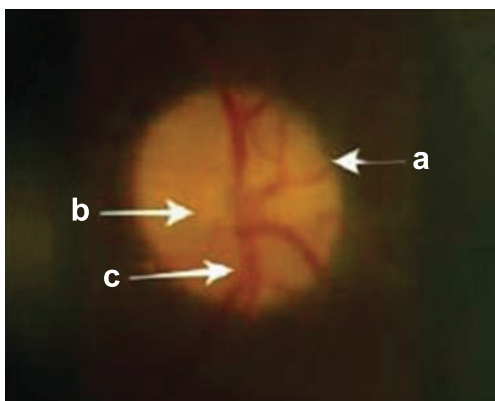


Fig. (1). Fundus photography taken from 90 diopter lens under slit lamp showing well-defined optic disc margin (a), pale disc with obliteration of cup disc ratio (b) and attenuated vessels (c). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

3.4. Antimicrobials

3.4.1. Chloramphenicol

Chloramphenicol is a broad-spectrum antibiotic that interferes with mitochondrial protein synthesis and is active against a variety of organisms. It can be used as either topical, intravenous, or oral. PN has been reported after a prolonged course (usually ≥ 6 weeks) of chloramphenicol with a cumulative dose of ≥ 100 mg. However, optic neuritis is the most associated neurotoxic complication. It usually leads to alterations in color perception and optic neuropathy, and in some cases, resulting in optic atrophy and blindness [239]. This has been observed in children with cystic fibrosis receiving relatively high doses for many months. The pathophysiology can be attributed to mitochondrial respiratory chain dysfunction. This drug, like ethambutol, causes an increase in mitochondrial calcium concentration through glutamate excitotoxic pathways. This leads to a decrease in mitochondrial respiratory chain function, along with vitamin B mechanism inhibition; it affects the function of Vitamin B12, however, serum concentration is normal. This mechanism is not very well understood. Given that the papillomacular bundles are the most susceptible to energy loss production since they possess a high concentration of mitochondria, this region is the earliest to be affected during the acute toxicity phase [239]. The visual loss in chloramphenicol toxic optic neuropathy may be sudden or subacute and painful or painless. Usually, limb paresthesia precedes the visual symptoms. The characteristic ocular findings are bilateral optic disc swelling, retinal vessel tortuosity and retinal hemorrhages. Surprisingly, the fundi may be normal. Typically, a pathognomonic centrocecal scotoma for toxic/nutritional optic neuropathies is seen. The differential diagnosis includes

nutritional optic neuropathy and Leber Hereditary Optic Neuropathy [239]. Most of these complications are reversible and attributed to a deficiency of B6 and B12 vitamins, and anecdotal improvement in symptoms after supplementation with vitamin B complex is reported. If optic neuritis develops, the drug should be discontinued immediately for a partial or complete reversal of symptoms [239].

3.4.2. Dapsone

Dapsone is an antimicrobial developed in 1908, and recently, it is being mostly used for dermatologic conditions given its anti-inflammatory property. In addition to its hematological side effect that appear early during treatment, it can also rarely cause neurologic manifestations, such as optic atrophy, sensory and motor peripheral neuropathies that have a more subtle onset. Symptoms usually appear after years of treatment; however, symptoms within 6 weeks have been reported [240]. The pathophysiology behind its toxicity is not really understood; it is thought to be due to its ability to concentrate in the nerve tissue leading to direct neurotoxicity. It affects motor fibers more than sensory fibers, mainly through axonal injury [241]. However, a secondary demyelinating neuropathy has been reported. Patients usually present with foot/finger drop, distal muscle atrophy, and sock and glove sensation loss. The toxicity is dose-dependent, usually requiring 25 to 600 g in cumulative doses, although lower doses have been reported to cause neuropathy. Electrophysiologic studies reveal an asymmetric finding of decreased Compound Muscle Action Potential (CMAP) amplitude with a possible increase in latency and velocity, predominantly distally [241]. A sensory deficit may be recorded. In very rare cases, dapsone can cause optic atrophy, even without optic neuritis (Fig. 1) [237]. Usually, patients have concomitant diabetes and dapsone-induced hemolysis, leading to the non-arteritic anterior ischemic optic neuropathy (NAION) by decreased blood flow and oxygenation to the optic head [240]. The increased prevalence of slow acetylators is not significant. Clinicians should have a baseline neurologic examination focusing on the sensory modalities, muscle mass and fine motor function with frequent assessment. NCS and EMG should be performed when needed [240, 241]. The treatment of neuropathy is the discontinuation of dapsone, with a possible resolution of symptoms after 1-3 years. Co-administration with cimetidine has not yielded protective results yet [241].

3.4.3. Ethambutol

Ethambutol is a synthetic bacteriostatic/bacteriocidal agent against *Mycobacterium tuberculosis*. Among its diverse side effects which are found in patients with kidney disease, hypersensitivity, PN, hyperuricemia, interstitial nephritis, retrobulbar optic neuritis are the most serious, despite occurring in around 6-15% of patients receiving the medication [242]. Most of the reported cases were reversible, however, a permanent damage in color recognition may persist. Two types of optic neuritis have been reported. The first affects the central fibers of the optic disc causing blurred vision, decreased visual acuity, central scotoma, and

frequently, a loss of the ability to distinguish green and red [242]. This is more common and dose-dependent. The second type, which is rarer, is seen with high doses and leads to peripheral visual field defects. Visual acuity and color vision are usually spared. The fundus is usually normal on examination [243]. The pathophysiology leading to toxicity is hypothesized to be related to ethambutol/zinc combination through chelation rather than zinc depletion per se. Toxicity has been reported with doses as low as 15mg/kg/d [244]. The maximum conventional dose for a healthy individual is 2mg/kg/d for 2 months, which is reduced to 15mg/kg/d to reduce the risk of optic neuropathy (ON). Dosage should be adjusted in CKD (15mg/kg/d) and ESRD (15mg/kg QOD) [244]. ON usually occurs 2 months post-initiation of treatment, however 3 cases in the literature report symptoms as early as 3 days from initiation of treatment [243]. Similarities between EMB induced ON and nutritional amblyopia have led to the use of parenteral hydroxocobalamin as treatment of ON, along with medication withdrawal. However, zinc supplementation has not shown any benefit. Many risk factors have been recognized that increase the chance of vision loss after EMB treatment [242-244]. First, the cumulative effects of isoniazid and ethambutol are more damaging when used together than when each is used alone. Second, impaired ability to excrete the drug increases the risk of side effects. Third, neuropathy is more frequent in geriatric patients [243]. Fourth, patients with plasma zinc levels below 0.7 mg/L display a higher incidence of neuropathy. Also, these side effects are more common when the dosage of EMB exceeds 15 mg/kg and with prolonged treatment duration. Last, patients having a history of alcohol abuse, compromised optic nerve head, or vascular disease are more prone to have side effects [243]. The Joint Tuberculosis Committee has placed guidelines for the prevention of EMB induced ON [244]. Routine visual acuity testing during treatment is generally not helpful in screening for ocular toxicity unless the patient complains of visual symptoms [242, 244]. MR brain can reveal abnormal signals in the optic tract/optic chiasm [243]. In addition, EMB can lead to a sensory more than motor axonopathy, detected by electrophysiologic studies. One case report was found regarding a patient on peritoneal dialysis developing ON, PN and laryngoparalysis [243, 244].

3.4.4. Fluoroquinolones (FQ)

Quinolones are antimicrobials that have a bactericidal effect by inhibiting DNA synthesis. Central Nervous System (CNS) toxicity is well recognized through a dose-related CNS excitation. This excitation is achieved by inhibition of γ -aminobutyric acid (GABA) receptors, and perhaps N-methyl-D-aspartate or adenosine receptors. In addition, tendinitis and tendon rupture are well-known side effects as well. PN is not a well-recognized side effect of FQ, which has been reported to occur in 1% of the patients receiving the treatment. In 2013, FDA included a black box warning for PN. The absolute risk of the condition with oral FQ exposure was 2.4 (95% CI, 1.8-3.1) per 10,000 patients per year, with symptoms appearing between 1-7 days after starting

the treatment [245]. The neuropathy can be seen up to 180 days after stopping the treatment; this side effect has been seen in the first 90 days and between 91- and 180-days post-exposure with a higher risk if FQs were used within both time frames. An increase in the estimated risk of neurotoxicity by 3% for every additional day of antibiotic use was also observed. This could be due to the mechanism of action of FQ, the delay in presentation and diagnosis, and the data registry [245]. The pathophysiology is not well understood. Patients usually present with small fiber neuropathy, mainly sensory symptoms consisting of numbness, tingling, prickling, burning pain, pins/needles sensation, "electrical" or shooting pain, skin crawling sensation, hyperesthesia, hypoesthesia, and allodynia. Less common motor deficits, such as weakness, twitching, fasciculations, tremors, spasms, and contractions are also observed. Objective findings of sensorimotor demyelinating features in electrophysiological studies have also been observed [246]. However, cases of carpal tunnel syndrome, sensorimotor axonal polyneuropathy and GBS have all been reported; GBS being more common with ciprofloxacin and levofloxacin, respectively, due to the vast use of these two antimicrobials. There are no clear-cut findings for the diagnosis of FQ-induced neuropathies except for the chronological pattern of the events [245, 246]. Age above 50, kidney disease, diabetes, use of other neurotoxic drugs, and possibly folate deficiency are risk factors for FQ-induced neuropathy. Sensory deficits can last up to 6 months (71%) or even 1 year (58%). Gabapentin and benzodiazepine usually help in symptom relief. Some suggest the use of folic acid as preventive measurement while using FQ and also to facilitate recovery [246]. However, the best approach would be to spare the use of FQ whenever possible and to decrease the duration of treatment. Steroid use is controversial, with some cases reporting improvement, and others reporting worsening of symptoms [245].

3.4.5. Nitrofurantoin

Nitrofurantoin is a synthetic antimicrobial which is used mainly in the treatment of urinary tract infections. It is a relatively safe drug. Side effects mainly affect the gastrointestinal tract, and it can be used for long-term low-dose prophylaxis of recurrent UTIs [247]. PN associated with its use is not very common. It is mostly seen in patients with kidney disease, possibly due to the added effect of uremia on the nerves and increased toxic serum level of the drug. On a dosage schedule of 300 mg per day, blood levels of 5.1 to 6.5 g/ml were reached in patients who had BUN levels greater than 45 mg, as compared with 1.8 to 2.2 g/ml in patients with normal BUN levels. However, adverse events were reported in patients with normal creatinine clearance [247, 248]. It is described as length-dependent large fiber sensorimotor polyneuropathy and small-fiber neuropathies. Patients usually present with a symmetrical sensory deficit in a glove and stocking pattern, along with associated loss of deep tendon reflexes weakness in the respective territories leading to intrinsic muscle atrophy in severe cases. Findings are prominent in the legs. Rarely, perineal paresthesia has been reported. There have been reported cases of retrobulbar

neuritis leading to scotoma, and another of fecal incontinence. Electrophysiological studies and sural nerve biopsy showed evidence of axonal sensorimotor polyneuropathy. Skin biopsy revealed swelling of nerve endings [248]. Additionally, cases of ganglionopathies/non-length-dependent polyneuropathy were reported, possibly by precipitating an autoimmune ganglionitis. Skin biopsy revealed a distinct pattern of epidermal denervation with either normal Intraepidermal Nerve Fiber Density (INFD) on all sites or loss of INFD proximally but preservation distally [247]. Fig. (2) shows skin biopsy findings. In the top part of the figure, baseline skin biopsy specimen from the distal leg is showing preserved epidermal fibers and clusters of abnormal axonal swellings in the dermis (arrows) that persisted after 6 months. Histologic studies of the spinal cord have shown demyelination of both dorsal and ventral roots but no inflammatory cells. Axonal chromatolysis of the anterior horn cells has been reported, and in one case, demyelination of the posterior column was noted. Histopathologic findings in the peripheral nerves included demyelination, Wallerian degeneration, and fusiform swelling of axis cylinders. A small percentage of patients showed slightly to moderately elevated spinal fluid protein [248]. The mechanism of toxicity is through axonal loss, and multiple theories have been implemented, including inhibition of acetyl coenzyme A synthesis, accumulation of nitrofurantoin metabolites (*e.g.*, semi carbazides [produced polyneuropathy in rats]) [247]. There are no reports that the drug affects vitamin B metabolism. Progression of symptoms is not dose-dependent. Symptoms usually start within 45 days of initiation of the medication, with the majority experiencing resolution of symptoms within a period of weeks following medication taper; however, prognosis is related to the severity of symptoms [248]. Medication should be immediately discontinued at the first sight of symptoms, and recovery, if achieved, may take up to 5 years to be complete [248].

3.4.6. Metronidazole

Metronidazole has potent bactericidal activity against anaerobes and protozoa. The drug is well-tolerated, with the most common side effects involving the gastrointestinal system. Rarely, CNS (convulsions, encephalopathy) and Peripheral Nervous System (PNS) manifestations have been reported. One case of optic neuropathy, one case of autonomic neuropathy, and two cases of ototoxicity were reported. PN is characterized by numbness, paresthesia in a stock and glove pattern, along with weakness and motor atrophy and decreased DTRs [249]. This deficit is caused by the binding of metronidazole and its metabolites to RNA, causing inhibition of protein synthesis. Other theories include competing with thiamine, causing nutrition deficiency-like neuropathy. The toxicity is both dose and duration dependent, involving around 50% of patients, requiring a dose of ≥ 42 g or at least 4 weeks of treatment. Neurotoxicity with lower doses and a short duration of treatment have been reported as well. The toxic range varies between 25-1080 g, and symptoms usually appear between onset and 180 days from initiation of treatment. Symptoms usually resolve after 3-7 days from stop-

ping the medication but can take up to years. PN starts earlier and lasts longer than CNS manifestations [249]. Electrodiagnostic studies usually reveal axonal sensory more than motor polyneuropathy. The drug should be discontinued immediately when neurotoxicity develops.

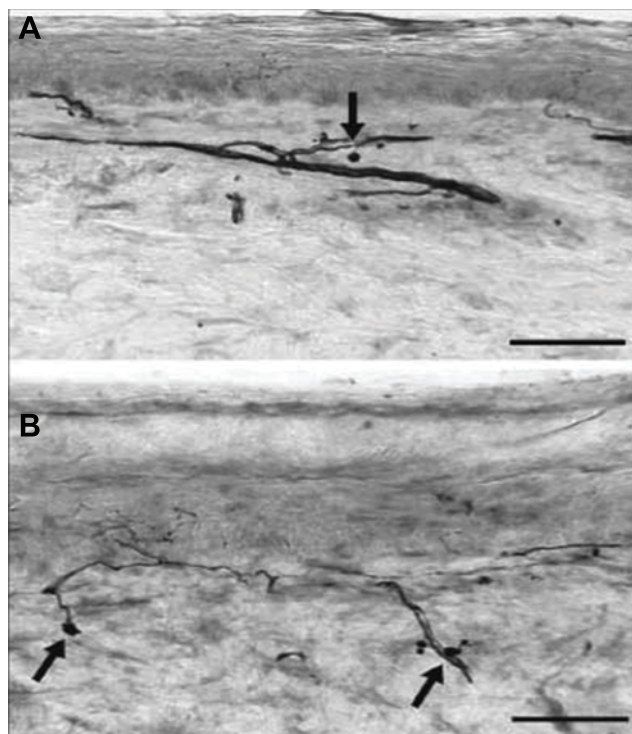


Fig. (2). Skin biopsy findings. (A) Staining was done with panaxonal protein gene product 9.5 (ubiquitinhydrolase; ABD Serotec). (B) The nerve fibers were immunostained with the panaxonal marker protein gene product 9.5. Scale bars indicate 50 μ m. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

3.4.7. Isoniazid (INH)

INH is one of the five medications used in the treatment of tuberculosis. Acute toxicity leads to neurologic symptoms, whereas chronic toxicity manifests as hepatotoxicity and PN [250]. The occurrence of PN with isoniazid is not uncommon. This side effect is dose-related, usually requiring doses more than 300 mg per day, and requiring more than 3 months of treatment. The occurrence is about 2-12% in patients treated with low or standard doses of isoniazid at 3-5 mg/kg/day and reaches 44% with increased doses of 16-25 mg/kg/day. It is even more common in patients with HIV. The pathophysiology is not well understood, and could be related to two mechanisms: the inhibition of pyridoxine-dependent enzyme systems leading to a decrease in the biologically active B6, or the direct inactivation of pyridoxine species by INH metabolites [250]. Symptoms usually manifest as paresthesia, muscle ache starting in the foot with possible involvement of the hands and arms, occasionally muscular weakness, and can progress to more severe symptoms such

as ataxia. As with chloramphenicol, toxic optic neuropathy has been reported, with similar findings: sudden painless blurry vision, color changes, and central scotomas [250]. Old age, slow acetylator status, diabetes, renal failure, alcoholism, malnutrition, HIV infection, chronic hepatic failure and pregnancy are known to be risk factors for isoniazid induced PN. NCS usually reveal a predominant sensory axonal neuropathy. Concomitant supplementation with pyridoxine is important in reducing and even preventing PN [250]. A complex outpatient rehabilitation program consisting of pharmacotherapy, educational sessions, breathing techniques, multi-modal exercise with neuromuscular proprioception techniques and psychological support had a positive effect on balance and gait [250].

3.5. Lithium

Lithium is a well-known treatment for various psychiatric disorders. Around 75% of the patients develop side effects from lithium toxicity, with 35-50% developing nervous system manifestations despite normalization of lithium levels [251]. The pathophysiology of lithium neuropathy is thought to be due to an intracellular accumulation of lithium and interference with the propagation of action potentials. However, lithium-induced neuropathy should be differentiated from lithium toxicity. The latter usually presents with spasticity, hyperreflexia, present Babinski sign, fasciculations and paresthesia. The sensation is usually normal. Toxicity is usually more prominent in patients on diuretics and angiotensin-converting enzyme inhibitors. Acute intoxication is a worse outcome, and this is related to the fact that lithium diffuses slowly in the CNS. Patients on chronic treatment have higher intracellular lithium concentrations. The hallmark of lithium-induced neuropathy is a sensorimotor axonal neuropathy [251]. Patients present with long tract neuropathy: decreased sensation in distal extremities, hypotonia and areflexia, with possible oculomotor abnormalities. Symptoms start 3-7 days even after normalization of lithium serum level, and clinical recovery takes weeks to months. Diabetes insipidus is commonly reported in these patients, and it may be either a risk factor for polyneuropathy, or a sign of acute intoxication; when present, the risk of neurotoxicity increases by 25 folds. Polyneuropathy can lengthen mechanical ventilation by an average of 4 days, rendering it important to wait for few days before proceeding to tracheostomy [251]. Extrarenal replacement therapy should be considered if lithium level is above 4 mmol/l with impaired renal function, or in the setting of neurologic involvement, given that lithium level barely correlates with neurotoxicity. When levels are above 5 mmol/l, Continuous Renal Replacement Therapy (CRRT), preferably hemodialysis is required regardless of kidney function. When lithium cannot be stopped, amiloride can be used for a lower risk of developing diabetes insipidus [251].

3.6. Phenytoin

Phenytoin is a hydantoin derivative and a first-generation non-sedative antiepileptic agent with anticonvulsant activity. It works by blocking voltage-dependent membrane

sodium channels responsible for increasing the action potential [252]. The adverse effects are diverse, including neurotoxicity. This type of toxicity is concentration-dependent, correlating with the total phenytoin level. It ranges from mild nystagmus to ataxia, slurred speech, vomiting, lethargy, and eventually coma and death. On the contrary, PN is the result of chronic (≥ 5 years) phenytoin use. It is important to differentiate between the immediate and reversible slowing of motor and predominantly sensory nerve conduction seen with high serum levels of phenytoin and the permanent electrical changes seen with chronic PN [252]. Data on phenytoin-induced PN is scarce, and the pathophysiologic basis of neuropathy is obscure. Patients usually present with areflexia and sensory deficit, mainly in the lower extremities. It is suggested that neuropathy is more common in patients with recurrent high drug serum levels and low folate [252]. The predominant electrophysiological finding among patients taking phenytoin at therapeutic levels was a reduction in the amplitude of the sensory action potential with relative preservation of the conduction velocity. In contrast, there is moderate slowing of conduction noted amongst those intoxicated with phenytoin. This suggests that the two effects on the peripheral nerve are distinct, although repeated episodes of the latter may ultimately lead to the former [252]. Slow metabolizers along with the use of CYP450 inhibitors are at increased risk of phenytoin toxicity, and the drug should be immediately discontinued in such cases. Despite being 90% protein bound, hemodialysis did not show a reduction in complications from toxicity, and until now, no antidote has been made. Activated charcoal should be considered if the patient presents early; however, the role of multiple-dose activated charcoal is controversial [252].

3.7. Cardiovascular Agents

3.7.1. Hydralazine

Besides the well-known effect of hydralazine on the cardiovascular system and lupus-like presentation, rare complications of the nervous system side effects, like peripheral neuritis/polyneuritis, have been reported [253]. The mechanism is thought to be the result of pyridoxine deficiency, leading to the formation of the pyridoxal-hydralazine complex [254]. The drug interacts with pyridoxal and can produce B6 deficiency; it also inhibits several enzymes requiring pyridoxal as a cofactor [253]. The symptoms usually appear as a reduction in light touch, pinprick and temperature in a glove and stocking distribution, decreased vibration and proprioception leading to a positive Romberg sign [254]. This side effect is usually dose and duration dependent [253]. However, polyneuritis can occur with low doses in the setting of low dietary B6, in slow acetylators, and in patients taking other medications leading to pyridoxine deficiency, mainly isoniazid [254]. Therefore, supplementation with B6 can be protective when high doses of the drug are required. In a study by Tedeschki *et al.*, symptoms appeared approximately 1 month after supplementation with 15mg of Hydralazine daily [254]. Usually, stopping the medication and supplementation with vitamin B6 are enough to reverse this side effect [253, 254].

3.7.2. Statins

Given their efficacy in lowering cardiovascular risks, statins are among the most prescribed medications worldwide. They lower cholesterol by reversibly inhibiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG--CoA) reductase and likewise reduce C-reactive protein levels, and may also decrease the levels of pro-inflammatory cytokines [255, 256]. In addition to the well-known myalgia caused by statin, they can induce neuropathic pain. This side effect is seen in 1.5-6.9% of the patients, especially in people with DM, middle-aged (age 50-64 years), living in rural regions as well as with exposure to specific toxins [256]. Additionally, more lipophilic statins (*e.g.*, simvastatin, lovastatin) are more likely to cause PN than less lipophilic statins (*e.g.*, pravastatin), possibly because of a higher affinity of the lipophilic drugs for nerves [255]. Longer exposure to statins has a chronic effect on the nerves and this may lead to the persistence of symptoms. Patients usually present with neuropathic pain, mainly tingling, burning, numbness, muscle or joint pain [256]. Motor deficits include generalized weakness, mainly associated with myalgia, and NCS show a sensorimotor axonal polyneuropathy [255]. The pathophysiology of this PN is related to decreased cholesterol levels leading to alteration in membrane synthesis, impairment of synapse formation, induction of apoptosis through GGPP, and a decrease in CoQ10 synthesis leading to neuropathic pain. However, contradictory findings regarding the role of statins in PN have been reported [256]. Preclinical studies have shown the role of statins in attenuating PN, which is independent of the cholesterol-lowering property. This is related to their anti-inflammatory and anti-free radicals generation properties. The difference in these two properties could be related to the dose of statins used. However, further human studies are needed [255, 256].

3.7.3. Procainamide

Procainamide, an antiarrhythmic agent used for the management of supraventricular and ventricular arrhythmias, is commonly associated with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [257]. It has been reported that procainamide can lead to PN. Symptoms typically start 1-4 years after initiating treatment, manifesting as paresthesia, panmodal sensory loss, proximal and distal symmetrical weakness, and areflexia. NCS show prolonged distal latency and reduced velocity, favoring demyelinating polyneuropathy. A nerve biopsy shows perivascular inflammation and onion bulb appearance. CSF can show elevated protein [257]. The prognosis is good with symptoms reversal after stopping the medication. Another rare adverse event is the exacerbation of myasthenia gravis. Procainamide can either induce, exacerbate, or reveal a previously undiagnosed MG. Patients do not have acetylcholine-receptor antibodies, and do not usually respond to edrophonium. This is probably explained by the drug's direct effect on the neuromuscular junction; it decreases the sensitivity of the post-junctional membrane to Ach. Furthermore, intravenous procainamide decreases postganglionic sympathetic neural activity leading to autonomic dysfunction [257]. Patients on amiodarone are

at increased risk of developing PN, in addition to systemic manifestations such as SLE.

4. MANAGEMENT OF PERIPHERAL NEUROPATHY

Keeping in mind that the treatment of PN varies by causality, the following medications are some of the most widely used in the field of therapeutics. Morphine is an opioid that acts on several central nervous system sites. The analgesic effect of opioids is due to their action on the brain, brainstem, spinal cord, and on peripheral terminals of primary afferent neurons. In the spinal cord, presynaptic and, to a lesser extent, postsynaptic μ -opioid receptors are found in the DRG. Modulating nociceptive transmission, leading to neuronal hyperpolarization, is enough to achieve analgesia. The analgesic effect is noted within one hour of administration, lasting for three to four hours. It increases the threshold for both cold evoked potential and mechanical evoked potential caused by CIPN from oxaliplatin, paclitaxel, vincristine, cisplatin and bortezomib. This effect has been significantly appreciated with vincristine [258]. However, morphine has been studied in the non-malignant type of pain and found to be efficacious for moderately improving pain. Nevertheless, it is not a first-line option for treatment given the over tolerability, possible development of tolerance to the analgesic effect and the risk of addiction. One study showed that the addition of low-dose gabapentin (10 to 20 mg/kg) to morphine (4 mg/kg) further decreased the pain score within 45-50 minutes compared to each drug alone [259]. Methadone, a potent μ (μ) agonist, is another opioid recently emerging as a treatment of PN. However, further clinical trials are still required [260]. The properties of methadone that set it apart from other opioids include the following: antagonism of NMDA receptors which modulate pain and attenuate morphine tolerance, reuptake inhibition of NE and serotonin similar to TCAs and SNRIs, and lack of active metabolites which decreases its side effects compared to morphine. It can be used for breakthrough pain given that the effect starts within 20 minutes, lasting for 4.5-6 hours [261]. This drug has been mainly studied and shown efficacy in diabetic neuropathy and phantom-limb syndrome. Opioid-naïve, frail, or elderly patients are initiated on low doses: 0.5-1 mg every 8 hours; the general population is started on 2.5-5 mg every 8 hours. Breakthrough pain can also be treated with methadone, and breakthrough pain dosing should be at least 10-20% of the total daily dosage, and it should be given every 3-4 hours as needed [261]. Δ^9 -tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, has an endocannabinoid transmitter system, binding to and activating cannabinoid CB₁ and CB₂ receptors. CB₁ is the primary cannabinoid receptor found in the CNS, whereas CB₂ is predominantly, but not exclusively, found in the immune system. Randomized, double-blinded, placebo-controlled studies have shown that cannabinoids exert a moderate improvement in neuropathic pain from diabetic neuropathy, phantom-limb syndrome, fibromyalgia, MS-related neuropathy, HIV associated neuropathy and CIPN (mainly from cisplatin and paclitaxel) [262]. However, some studies report that the adverse effects of cannabinoids (somnia-

vomiting, UTI, relapse of MS) outweigh their benefits, therefore, they should be used with caution. To date, there is no consensus on the use of cannabinoids in PN, and further high-quality trials of long-term exposure to cannabinoid-based medications, together with careful monitoring of patients, are required to better characterize safety issues related to the use of medical cannabinoids.

There is currently general agreement placing antidepressants, tricyclic antidepressants (TCA), Serotonin-Noradrenaline Reuptake Inhibitors (SNRI), and anticonvulsants acting at calcium channels, Pregabalin and Gabapentin, as first-line treatment. Despite their efficacy, opioids are not considered the first choice because of adverse drug reactions and concerns regarding abuse, diversion, and addiction [263].

TCAs act by inhibiting the neurotransmission between nociceptors, first order neuron, and spinothalamic neurons, second order neuron, by inhibiting the reuptake of serotonin and norepinephrine through the descending inhibitory fibers from the brainstem to the spinal cord. They can also activate interneurons that release GABA and endogenous opioids in these synapses. Last, they have a long-term effect by acting peripherally on the dorsal root ganglia. TCAs also have sodium channel blocking properties and can be used topically for analgesia. They have been proven efficacious in the treatment of painful polyneuropathy, painful diabetic neuropathy, post-herpetic neuralgia, peripheral nerve injury, and CIPN, mainly Vinca alkaloids, platinum-based or Taxane-induced PN [264]. Despite these benefits, this class of medications has many adverse drug reactions. The two main ones are its anticholinergic effect and cardiotoxicity, rendering their use more restricted. It is worth noting that nortriptyline is more noradrenergic than amitriptyline, and thus has fewer side effects [265].

Duloxetine, a selective SNRI, has been found efficacious in the treatment of painful peripheral neuropathy (PPN). At a dose of 60 mg daily, it achieved better results with Cisplatin-induced PN vs. Taxane-induced PN with less severe adverse events, mainly nausea, constipation, and fatigue. It acts by augmentation of serotonin and norepinephrine mediated inhibitory pathways in the CNS. Venlafaxine is another SNRI used off-label in the treatment of PPN. It is less efficacious than duloxetine, with side effects including elevated blood pressure [266].

Pregabalin and Gabapentin are anticonvulsants acting on the $\alpha 2 -\delta$ (alpha 2 -delta) subunit of the voltage-gated calcium channels present on the presynaptic terminals in the brain and spinal cord, controlling neurotransmitter release [267]. In nerve injury, these calcium channels are overexpressed. These drugs act by internalizing these channels, hence modulating pain. Given the higher affinity of pregabalin to these channels, it has a higher analgesic potency than gabapentin. This was mainly seen in Taxane-induced PN as one study suggested the superiority of pregabalin to duloxetine in Taxane-PN [268]. It is worth noting that Gabapentin at 2700 mg/d exhibited no significant reduction in pain from CIPN compared to Pregabalin at 300 mg/d. In general, these drugs are well tolerated. Adverse effects in-

clude dizziness and somnolence, more with gabapentin use, and they can be safely used with other analgesics given that they are not substrates of cytochrome P450.

In a study comparing their efficacy in pain modulation, Nortriptyline showed the highest efficacious percentage (25%) and the second-lowest quit rate (38%). Duloxetine had the second-highest efficacious rate (23%) and the lowest drop-out rate (37%). Pregabalin had the lowest efficacy rate (15%). Gabapentin and venlafaxine were not included in this study [263]. However, multiple recent studies have revealed no significant benefit of TCAs in PPN, and updated 2020 guidelines from ASCO have listed no recommendations for their use outside clinical trials.

Last, some agents have already gained the level of evidence in Oxaliplatin-induced PN such as Calcium/Magnesium (Evidence I, E) and Carbamazepine (Evidence II, E), and in Taxane-induced PN, such as cryotherapy (Evidence II, C) [269]. Table 2 and Fig. 3 present a summary related to the peripheral neuropathy caused by some of the common drugs discussed in this manuscript. Table 3 presents the recommended treatment of peripheral neuropathy in different settings.

5. NOVEL OPTIONS

5.1. Refrigeration Methods

Since chemotherapy-induced peripheral neuropathy (CIPN) can have a negative impact on the patient's quality of life (QOL), and may lead to dose reduction, dose delay or treatment cessation, many prevention and treatment modalities have been investigated. Recent studies have suggested the clinical utility of limb hypothermia or cryotherapy as a preventive measure of CIPN [34, 270]. The reason behind cooling methods comes from the successful use of scalp cooling to prevent chemotherapy-induced alopecia, as the low temperature induces vasoconstriction of capillaries leading to decreased microvascular perfusion and subsequent decrease in the delivery of chemotherapeutic agents to the localized cooled tissue [271]. The most frequently used conventional cooling modalities are ice gel packs and frozen gloves [272, 273]. Despite the latter showing promising results [270, 274], these frozen gloves are unable to provide thermoregulation, resulting in poor tolerability and frostbite [270].

A retrospective study demonstrated that the incidence of docetaxel-induced peripheral neuropathy dropped from 57% in patients who did not use frozen gloves and socks to 35% in patients who wore them [270]. On the other hand, Scotte *et al.*'s study reported that 11% of patients dropped out due to cold intolerance [275]. Another study that compared cryotherapy, using a frozen glove, and compression therapy, using a surgical glove (SG), found no difference of outcomes in terms of prevention of nab-PTX-induced PN [276, 277]. Cooling modalities [37] offering thermoregulation have been developed and shown to be of therapeutic value for sports injuries and orthopedic surgery [278, 279]. A small study that included 20 breast cancer patients who received weekly paclitaxel (PTX) along with continuous-flow

Table 2. Relationship among medications and peripheral neuropathy.

Medication	Concentration	Incidence Rate of PN	Time to Onset	Time to Resolution Following Taper	Management
Nitrous oxide (NO)	40-60% of inspired air	3%- 5%	1-11 hours	3-12 months	Withdrawal + Vitamin B12
Disulfiram	Dose-dependent, starting 250 mg/d	1:15000	4-8 weeks	Unknown, given the underlying alcohol induced PN	Withdrawal
Colchicine	1-2 mg/d, lower in kidney and liver failure	1%- 2%	Acute (overdose) chronic (weeks to months)	Months to years	Fluid resuscitation and correction of electrolytes. Charcoal use only prior to GI symptoms
Chloramphenicol	Cumulative dose of >100 mg	Rare	6 weeks	Vision: 4- 6 weeks PN: 4- 8 weeks	Withdrawal, B complex supplement
Dapsone	25 to 600 g in cumulative dose	Unknown	6 weeks to 5 years	1- 3 years	Withdrawal
Ethambutol	15 mg/kg/d	Unknown	3 d to 3 months	1- 3 years. 50% have permanent residual deficit	Withdrawal. No benefit of Zinc supplementation
Fluoroquinolone	Dose-dependent	2.4/10000	1-90 days 91-180 days	6 months to 1 year	Withdrawal, Gabapentin or benzodiazepines. Controversial use of steroids
Nitrofurantoin	Serum concentration of 1.8 to 2.2 g/ml	0.5%- 1%	Within 45 days	Few weeks to 5 years	Immediate withdrawal
Metronidazole	Cumulative dose of 25-1080 g	1.7%- 17.9%	7-180 days	7 days to years	Withdrawal
Isoniazid	>300 mg/d	2%- 12% with low doses, 44% with high doses	>3 months	Motor improvement in few months, sensory deficit may persist up to years	Pyridoxine supplementation, complex rehabilitation program
Lithium	Dose and duration dependent. Acute toxicity if level> 4 mmol/l.	Unknown	3-7 days	Weeks to months	Withdrawal, extrarenal replacement therapy if level> 4 mmol/l. Amiloride if lithium cannot be stopped
Phenytoin	Cumulative dose	Unknown	> 5 years	Further follow up is needed	Active charcoal
Hydralazine	15 mg daily	Unknown	Within 1 month	Within weeks	Vitamin B6
Statins	Dose and duration dependent.	1.5%- 6.9%. 4-14x higher with concomitant steroid use.	Weeks to months	Variable	Drug cessation
Procainamide	Dose and duration dependent	8%	1- 4 years	Weeks to months	Withdrawal

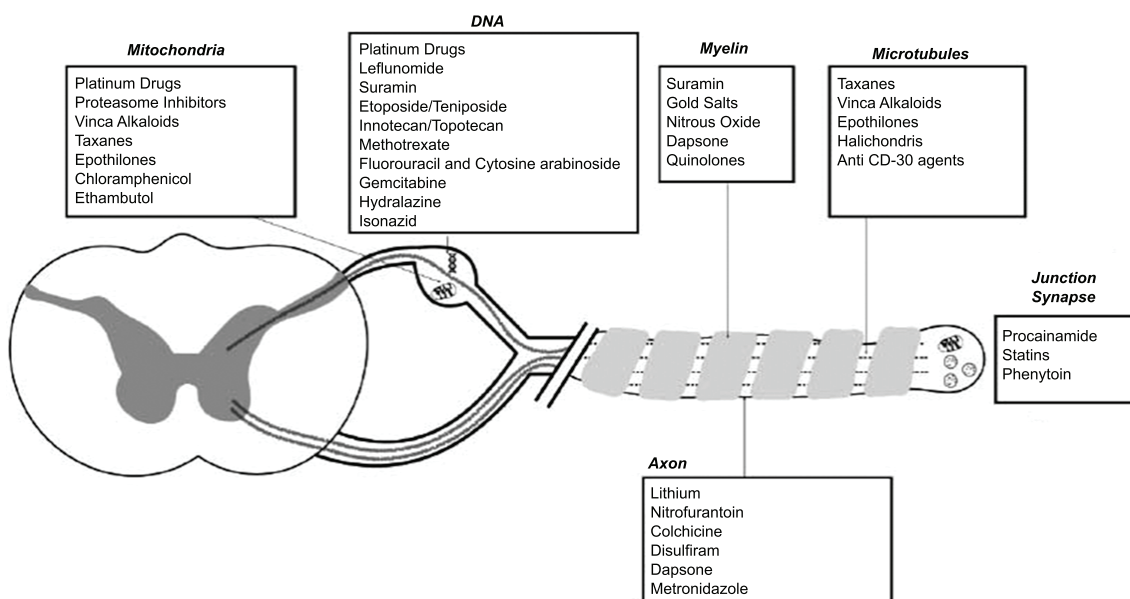


Fig. (3). The level at which each drug affects neurons. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 3. Recommended treatment of peripheral neuropathy in different settings.

-	Medication Class	Starting Dose	Titration	Maximum Dose	Duration of Adequate Trial	Best Used in
TCAs	Amitriptyline, Nortriptyline	25 mg at bedtime	increase by 25 mg/d every 3-7 d as tolerated	150 mg/d, or as long as blood concentration <100 mg/L	6-8 weeks with 2 weeks at max dose	Amitriptyline: treatment of mild mechanical allodynia of oxaliplatin. Nortriptyline: cisplatin-induced PN. No effect on paresthesia.
SSNRIs	Duloxetine	30 mg once daily	increase to 60 mg daily after 1 week	60 mg twice daily (no benefit over 60mg daily)	4 weeks	Treatment of pain, tingling and numbness of platinum> taxanes induced PN. Diabetic neuropathy
	Venlafaxine	37.5 mg once or twice daily	increase by 75 mg every week	225 mg/d	4-6 weeks	Prevention of oxaliplatin-induced PN
Calcium channel α_2 - δ ligand	Gabapentin	100-300 mg at bedtime	increase 100-300mg 3x daily every 3-7 d	3600 mg/d (1200mg 3x daily). Reduce in renal impairment	3-8 weeks for titration, plus 2 weeks at max dose	Paclitaxel, oxaliplatin
	Pregabalin	50 mg 3x daily or 75 mg 2x daily	increase to 300 mg/d after 3-7d, then by 150 mg/d every 3-7d as tolerated	600 mg/d (200 mg 3x daily or 300mg 2x daily. Reduce if renal impairment	4 weeks	Vincristine, paclitaxel, oxaliplatin
Opioid agonist	Morphine	10-15 mg every 4h as needed	after 1-2 weeks, convert daily dose to long-acting opioid, with short acting medication as needed	No maximum dosage. Refer to pain specialist if daily dosage >120-180 mg/d	4-6 weeks	Second-line treatment
	Tramadol	50 mg once or twice daily	increase by 50-100 mg divided every 3-7 d	400 mg/d (100 mg 4x daily). If >75y, 300 mg/d	4 weeks	Second-line treatment

limb hypothermia at a coolant temperature of 22 °C, revealed that the CIPN was grade 0 in 4 patients (20%), grade 1 in 12 patients (60%), grade 2 in 2 patients (10%), and grade 3 in 2 patients (10%) [280].

5.2. Hilotherm

Hilotherm is a regional cooling system which forms a closed-loop system with large, cooled cuffs that cover the hands up to the wrist, and the feet up to the ankles, and tubes connected to the device, through which a continuous coolant flows at a temperature of 10 °C [281]. The efficacy and safety profile of Hilotherapy for the prevention and symptomatic relief of CIPN has been assessed in a single-arm, single-center, retrospective study conducted at Poliambulanza Hospital, Germany. 64 patients with breast, gynecological, and pancreatic cancer, received weekly paclitaxel (PTX), PTX/carboplatin, and nab-paclitaxel (nab-PTX)/ gemcitabine as indicated for their proper therapeutic scheduled dosage. Of these, 54 (84%) patients completed all cooling cycles using Hilotherm. Continuous cooling was well tolerated by all patients, and no patient had grade>2 CIPN evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. at the end of each cooling session [281]. In addition, no serious or lasting adverse events were encountered as a result of Hilotherapy. This study shows that continuous cooling using Hilotherm is well tolerated and safe, despite some study limitations which include it being a single-center, single-arm trial without a direct comparator, and having decreased sample size [281]. More research is needed to implement such helpful strategies to prevent painful CIPN in clinical settings.

6. ONGOING TRIALS ASSESSING FURTHER OPTIONS

Although many prophylactic agents have been proposed against CIPN, very few have been tested in animals and humans. More than 40 randomized clinical trials of preventative therapies have been investigated without any conclusive evidence. The challenge is due to the multiple mechanisms leading to CIPN and the effect of the treatment on antitumor properties of the chemotherapy.

Recent studies have shown that knockout of transporters localized to the DRG in mice, such as OATP1B2 (OATP1B1 in humans), organic cation transporter novel type (OCTN2) and OCT2, protects against CIPN associated with paclitaxel, vincristine, and oxaliplatin [282]. Sensitive blockers of these transporters are tyrosine kinase inhibitors. Other agents like Nilotinib, an OATP1B2 inhibitor, and Dasatinib, an OCT2 inhibitor, have demonstrated that inhibiting these transporters could provide neuroprotection against paclitaxel and oxaliplatin induced PN without affecting systemic drug clearance or negatively influencing antitumor efficacy. The hypothesis is being tested in a double-blinded, placebo-controlled, randomized phase II study [283].

Calmangafodipir, derived from mangafodipir, a magnetic resonance imaging contrast agent, reduces reactive oxygen species by mimicking manganese superoxide dismutase, a mitochondrial enzyme against oxidative stress [284]. Positive randomized phase II study and phase III study (POLAR programme) are ongoing, and have shown promising results with platinum agents. It may also be possible with other chemotherapeutic classes as well [284, 285]. It reduced cold allodynia and other sensory symptoms during and after treat-

ment. Preclinical data in rodents also suggest that administration of carvedilol, a cardioprotective drug reduced levels of nitrotyrosine, and subsequently, increased expression of mitochondrial superoxide dismutase in both sciatic nerves and DRG tissues [286].

The voltage-gated sodium channel 1.7 (Nav1.7) plays an important role in multiple preclinical models of neuropathic pain and in inherited human pain phenotypes. In preclinical models, utilization of peripheral sodium channel blockers targeting Nav1.7 was able to reverse hyperalgesia and allodynia without damaging motor function [287]. Recent studies have shown that Nav1.7 is only increased in DRG neurons of the affected dermatomes. A randomized, double-blind placebo-controlled crossover pilot study investigating the Nav1.7 antagonist, XEN402, showed that patients with inherited erythromelalgia experienced 42% less pain from Nav1.7 blocking than placebo [287].

Another trial involved 6 patients who received an average of 21.5 combined electrochemical treatments (CET) over a 6 to 12 weeks time period [288]. These patients were followed for a total of 4 to 40 months after treatment with an average of 26 months. It was shown that 5 of 6 patients receiving CET regenerated their nerve density by 100%, reduced their pain scores by 90%, restored their function by 74% and had no side effects. This is a promising technique for PN that also needs further validation [288].

Molecules that can prevent axonal injury are also being investigated. In preclinical rodent models, ethoxyquin prevented paclitaxel- and cisplatin-induced distal axonal degeneration *via* HSP 90 modulation, without compromising antitumor efficacy. Clinical trials are currently being considered. In addition, modulation of BCL-w levels might represent another strategy against Paclitaxel-induced PN by the interaction of IP3 receptor on the neurons. Second, the reduction of APE1 expression in sensory neurons increases neurotoxicity. Targeting APE1 by small-molecule APX3330 is protective against CIPN while also having *denovo* antitumor efficacy. APX3330 is undergoing human clinical trials as an antineoplastic agent as well as for the prevention of CIPN. Third, Fingolimod, used in the treatment of multiple sclerosis, has been used in preclinical animal models. Oral administration of Fingolimod can prevent and treat neuropathic pain from a variety of chemotherapeutic agents; this has been achieved without the development of tolerance to an analgesic effect and without interfering with antitumor efficacy of chemotherapy. However, it may have synergistic antitumor properties, and more clinical trials are required. Nicotine has also been discussed as a possible solution. Nicotine is known for its downstream effect on the NF- κ B pathway and its ability to inhibit neuronal apoptosis and astrocyte activation. Both prevention and treatment of paclitaxel-induced PN are also being investigated as well [289].

CONCLUSION

Even though this review focuses on chemotherapy-induced PN and some major drugs that also cause PN, many more medications are known to cause PN. The wide possi-

ble arrays of pathophysiological mechanisms raise the bar to discover treatment options for each family of drugs [229]. Patients presenting with PN should be definitely asked about recent medication administration as early intervention can prevent significant axonal injury. Some drug-induced PN are potentially reversible if discovered early. The pathophysiology by which CIPN occurs is distinguished from other causes of drug-induced PN in that the former affects cell structures and ongoing processes. CIPN affects microtubules, mitochondria, and cell nuclei. Other ways include altered ion channel activity, myelin sheath damage, immunological processes and neuroinflammation [31]. Even though CIPN is reversible, 30% of patients still complain of ongoing symptoms 6 or more months after stopping the medication. Ongoing studies are evaluating the use of different medications to decrease the severity or even prevent CIPN. Vitamin E, glutamine, alpha-lipoic acid, and glutathione have all been assessed so far. More research will hopefully unravel the optimal management plan [56].

AUTHORS' CONTRIBUTIONS

M.B.Z. and H.A. drafted the manuscript. M.B.Z. and D.M. and G.D. contributed to the discussion section. All authors proofread the manuscript. H.A. conceived the idea for the paper. All authors have read and approved the final manuscript.

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