Current Clinical Pharmacology, 2020, *15*, 38-48

REVIEW ARTICLE

Drug-Induced Peripheral Neuropathy: A Narrative Review

Mark R. Jones[1,*], Ivan Urits[1], John Wolf[2], Devin Corrigan[2], Luc Colburn[2], Emily Peterson[2], Amber Williamson[2] and Omar Viswanath[3]

[1]*Harvard Medical School, Beth Israel Deaconess Medical Center, Department of Anesthesia, Critical Care, and Pain Medicine, Boston, MA, 02118, United States;* [2]*Creighton University School of Medicine-Phoenix Regional Campus, St. Joseph's Hospital and Medical Center, Phoenix, AZ 85013, United States;* [3]*Valley Anesthesiology and Pain Consultants, Phoenix, AZ, University of Arizona College of Medicine-Phoenix, Phoenix, AZ, Creighton University School of Medicine, Omaha, NE, United States*

Abstract: ***Background***: Peripheral neuropathy is a painful condition deriving from many and varied etiologies. Certain medications have been implicated in the iatrogenic development of Drug Induced Peripheral Neuropathy (DIPN) and include chemotherapeutic agents, antimicrobials, cardiovascular drugs, psychotropic, anticonvulsants, among others. This review synthesizes current clinical concepts regarding the mechanism, common inciting medications, and treatment options for drug-induced peripheral neuropathy.

Methods: The authors undertook a structured search of bibliographic databases for peer-reviewed research literature using a focused review question and inclusion/exclusion criteria. The most relevant and up to date research was included.

Results: Drug-induced peripheral neuropathy is a common and painful condition caused by many different and frequently prescribed medications. Most often, DIPN is seen in chemotherapeutic agents, antimicrobials, cardiovascular drugs, psychotropic, and anticonvulsant drugs. Certain drugs exhibit more consistent neuropathic side effects, such as the chemotherapeutic compounds, but others are more commonly prescribed by a larger proportion of providers, such as the statins. DIPN is more likely to occur in patients with concomitant risk factors such as preexisting neuropathy, diabetes, and associated genetically predisposing diseases. DIPN is often difficult to treat, however medications including duloxetine, and gabapentin are shown to reduce neuropathic pain. Advanced techniques of neuromodulation offer promise though further randomized and controlled studies are needed to confirm efficacy.

Conclusion: Awareness of the drugs covered in this review and their potential for adverse neuropathic effect is important for providers caring for patients who report new onset symptoms of pain, paresthesia, or weakness. Prevention of DIPN is especially important because treatment often proves challenging. While many pharmacologic therapies have demonstrated analgesic potential in the pain caused by DIPN, many patients remain refractive to treatment. More studies are needed to elucidate the effectiveness of interventional, neuromodulating therapies.

ARTICLE HISTORY

Received: October 23, 2018
Revised: December 03, 2018
Accepted: January 11, 2019

DOI:
10.2174/1574884714666190121154813

Keywords: Drug induced peripheral neuropathy, chemotherapy, statins, gabapentinoids, pain, paresthesia, weakness.

1. INTRODUCTION

Drug-Induced Peripheral Neuropathy (DIPN) occurs when a chemical substance causes damage to the peripheral nervous system [1]. DIPN is potentially irreversible, resulting in sensory deficits and paresthesia typically in a glove and stocking type distribution; motor involvement is rare. The onset of signs and symptoms usually takes weeks to months, as dose-dependent onset requires neurotoxins to build up and reach peak concentrations in the bloodstream. The neurotoxins can affect and modify both peripheral neurons and glial cells through a variety of mechanisms [2]. With rising neurotoxin levels, axonal distal degeneration occurs not dissimilar to a demyelinating process. DIPN accounts for only 4% of all neuropathies, yet 60% of patients undergoing chemotherapy will develop DIPN [2, 3].

2. PATHOPHYSIOLOGY

Most drug-induced peripheral neuropathies cause damage at the dorsal root ganglia. Six mechanisms of peripheral nerve injury have been described in relation to peripheral neuropathy including metabolic dysregulation, covalent

*Address correspondence to this author at the Beth Israel Deaconess Medical Center, Department of Anesthesiology, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215; Tel: 617-278-8000;
E-mail: mjones13@bidmc.harvard.edu

2212-3938/20 $65.00+.00

modification, organelle damage, intracellular inflammatory signaling, axonal transport defects, and channelopathies [4] Metabolic dysregulation is specifically related to diabetic peripheral neuropathy and will not be discussed further in this paper.

A covalent modification is thought to induce pathology through DNA modification, particularly in drugs containing platinum. A study involving cisplatin, a platinum-containing medication, demonstrated that cisplatin binds dorsal root ganglia sensory neuronal DNA 10 fold greater than a neuron-like dividing cell line. Platinum accumulates in peripheral neurons, covalently binds to DNA and interferes with replication, eventually resulting in apoptosis and sensory neuropathy [5].

Organelle damage is associated mainly with mitochondrial and endoplasmic reticulum damage. Chemotherapy drugs in the taxane family target microtubule depolarization and in turn affect mitochondrial and endoplasmic reticulum function. As microtubules depolarize, calcium channels on endoplasmic reticulum open, which causes mitochondrial permeability transition pores to open. This releases reactive oxygen species and cytochrome C, ultimately initiating apoptotic pathways [6].

Intracellular inflammation can be seen in both chemotherapy-induced peripheral neuropathy and HIV-induced peripheral neuropathy. The inflammation from chemotherapy drugs is linked to organelle damage and apoptotic death of the neuronal cell, leading to an overall inflammatory state in the nerve. HIV's interactions with gp120 induce inflammation and activation of the complement cascade, damaging dorsal root ganglia and leading to neuronal cell death [7].

Axonal transport defects occur *via* interactions of microtubule depolarization with organelle damage induced by drugs such as paclitaxel, cisplatin, and borezomib [8]. Borezomib prolongs proteasome inhibition in addition to increaseing alpha-tubulin polymerization, which results in the death of rapidly dividing cells [8].

As previously discussed, channelopathies may result from microtubule polymerization interference and subsequent calcium channel dysregulation. Sodium channels are also subject to interference by several drugs. Oxaliplatin, for instance, increases sodium currents and prolongs the cell's refractory period, while having no effect on potassium channels [9].

3. DIAGNOSIS

The diagnosis of DIPN remains a diagnosis of exclusion, mainly based on the patient's history. The clinician needs to consider DIPN especially in the setting of recent initiation of drugs known to cause neuropathy, such as a chemotherapeutic agent. As stated previously, patients typically present with paresthesia in a stocking-glove distribution week to months after starting a new drug regimen [2]. Interestingly, risk factors for DIPN vary by individual drug. For instance, risk of DIPN with brentuximab does not increase with factors such as sex, age, diabetes mellitus, BMI, or prior underlying neuropathy [10]. Taxane-induced peripheral neuropathy, on the other hand, demonstrates increasing risk with demographic factors such as age, neuropathy at baseline, smoking, and diabetes [11]. DIPN, while mainly a clinical diagnosis, will exhibit an axonal pattern of damage on both motor and sensory nerve conduction studies [12].

4. CARDIOVASCULAR AGENTS

4.1. Amiodarone

Amiodarone is a class III anti-arrhythmic used to prevent numerous arrhythmias of atrial and ventricular origin. Although the medication has several known adverse effects on the lungs, thyroid and eye, peripheral neuropathy has not been characterized to the same degree. A recent study examining amiodarone use in 45,173 patients found the incidence rate of peripheral neuropathy to be 2.38 per 1000 person-years [13]. A previous study of 707 amiodarone-treated patients noted only 2 patients who experienced peripheral neuropathy [1]. The greatest risk factors were found to include increased dose and duration of therapy, with affected patients exhibited both sensory and motor deficits. Previous investigations on amiodarone-induced peripheral neuropathy attributed such deficits to both demyelination and axonal loss with lysosomal inclusions. Recent findings have further characterized the degenerative process, suggesting the contribution of enhanced oxidative stress and impaired lysosomal degradation within Schwann cells as an additional component to the neuronal pathogenesis [14].

4.2. Statins

The Statin class consists of HMG-CoA reductase inhibitors, including simvastatin, pravastatin, and fluvastatin. Although these are universally prescribed for the reduction of cardiovascular disease and mortality, long-term use of statins can result in adverse effects such as peripheral neuropathy. Previous cohort studies have shown an increase in the incidence of DIPN in patients treated with statins, and increased duration of treatment appears to be a significant risk factor in the development of sensory neuropathy. In a population of 1,084 patients diagnosed with peripheral neuropathy, an odds ratio of 4.6 was found for patients treated with a statin, while another study of 2,040 patients with statin exposure reported an odds ratio of 1.19 for development of peripheral neuropathy [1]. While there is a lack of recent significant research, a study comparing sensory perception among 30 statin-treated patients against patients without statins demonstrated decreased vibration perception in the study group, suggestive of peripheral sensory neuropathy [15] In a recent case-control study, sensory and motor wave features in peripheral nerves were evaluated in 39 patients who had received statin treatment using electrodiagnosis. While there was no significant difference in peripheral neuropathy as defined clinically, the amplitude of peroneal motor and sural sensory nerve responses exhibited significant differences. Additionally, a 2017 meta-analysis of 3,104 patients from 1999 to 2013 showed no association between history of statin use and increased risk of idiopathic polyneuropathy [16].

To date, the pathogenesis of statin-induced peripheral neuropathy is not well understood. Current theories surmise that the inhibition of cholesterol synthesis and alterations of

Table 1. Characteristics of cardiovascular agent-related DIPN.

Agent Group	Drug Dosage	Incidence	Risk Factors	Pathogenesis	Neuropathy Type
Statin	Increased treatment duration and cumulative dose associated with increased polyneuropathy relative risk [17]	Odds ratio: 1.2-4.6	Duration of treatment >2 years	alterations of membrane function, disruption of ubiquinone synthesis and energy utilization in nerves	Primarily sensory neuropathy
Amiodarone	>200 mg has highest association with DIPN [19]	2/707 patients 2.38/1000 person-years	Increased dose, length of drug therapy	Demyelination, loss of large axons with lysosomal inclusions; oxidative stress and impaired lysosomal degradation	Sensory and motor, chronic

membrane function within nerves disrupts ubiquinone synthesis, subsequently disturbing energy utilization within neurons [17]. While clinical data has shown statins to be neuropathic pain-inducing, pre-clinical data has shown statins to be neuropathic pain attenuating – possibly attributed to cholesterol independent inhibition of the inflammatory cascade and free radical generation [18]. While the significant cardiovascular benefit of statins still appears to outweigh the risks of peripheral neuropathy development, further research is needed to better understand the pathogenesis and clinical manifestations [19]. Table **1** lists the characteristics of cardiovascular agent-related DIPN.

5. CHEMOTHERAPEUTIC AGENTS

5.1. Vinca Alkaloids

The Vinca alkaloids are chemotherapeutics used for the treatment of hematologic, lymphatic, and gynecologic malignances, as well as solid tumors. Among this class of therapies, vincristine is associated with the greatest incidence of neurotoxicity, although studies have also reported DIPN in patients treated with vinorelbine and vinblastine [20]. In afflicted patients, the neuropathy typically manifests in the distal lower extremities and progresses proximally. Changes in sensation are characterized by decreased touch, vibration, and temperature sensations as well as paresthesia and diminished deep tendon reflexes (DTR) [21]. Higher single dose and cumulative drug concentration are predictive risk factors for the development of DIPN, but the incidence varies widely due to the lack of standardized patient assessment and grading of severity. In pediatric populations, studies report as high as 96% of patients developed some degree of vinca-induced DIPN, with incidence rates ranging from 0% to 37% for grade 3 or 4 [21]. While the pathogenicity is not yet fully understood, a proposed mechanism suggests a polymerization dysfunction within axonal microtubules as a contributory mechanism [21].

5.2. Platinum

All platinum chemotherapeutics are characterized by chronic sensory neuronopathic effects *via* accumulation in the dorsal root ganglion, with an incidence of 30-40% in patients treated by oxaliplatin and cisplatin [22, 23]. Risk relates to higher cumulative dosing, and a "coasting" phenomenon may be observed as effects tend to worsen in the months after stopping treatment. In addition to the long-term manifestations, Oxaliplatin is also associated with acute,cold-induced neuropathic pain. The mechanism of chronic pathogenesis with cisplatin involves damage to dorsal root sensory neurons mediated by irreversible cross-linking to DNA and neuronal apoptosis, while the acute toxicity seen with oxaliplatin is attributed to voltage-dependent sodium channel dysfunction [20].

5.3. Bortezomib & Thalidomide

Thalidomide and Bortezomib are both used in the treatment of multiple myeloma. Higher cumulative doses and longer treatment durations are risk factors for the development of DIPN. Incidence has been reported between 23% and 70% with thalidomide treatment, up to one third of patients grade 3-4, and between 37% and 64% in bortezomib treatment with up to 13% grade 3-4 [24, 25]. While both cause a predominantly sensory neuropathy, thalidomide is characterized by prominent paresthesia in the hands and feet along with numbness and mild motor dysfunction. Bortezomib shows distal paresthesia and numbness especially in the lower limbs, along with substantial small c-fiber involvement presenting as sharp or burning pain in the feet [26]. While the mechanism of pathogenesis appears multifactorial, bortezomib is shown to promote mitochondrial calcium release leading to apoptotic cascade activation and interference with microtubule stabilization. A recent study by Yin *et al*. proposes that bortezomib-induced neuropathy generates from activation of Activating Transcription Factor 3 (ATF3) in primary cultured Dorsal Root Ganglion (DRG) neurons and in DRG, as demonstrated in painful peripheral neuropathic rats [27]. Thalidomide's neurotoxicity may be related to antiangiogenic activities, among other potential mechanisms [24].

5.4. Epothilones

Epothilones such as ixabepilone are used in the treatment of advanced breast cancer as well as refractory prostate cancer. Risk factors for the development of DIPN include dose per treatment cycle, duration of infusion, and cumulative dose [28]. The neuropathy is predominantly sensory and cumulative, and all-grade incidences ranged from 15% in the neoadjuvant setting to 64% with monotherapy for the treatment of metastatic breast cancer [28]. The mechanism of pathogenesis is unclear, but the neurotoxicity profile is similar to that of other microtubule-stabilizing agents such as taxanes [28].

Table 2. Characteristics of chemotherapeutic agent-related DIPN.

Agent Group	DIPN Dosage	Incidence	Risk Factors	Pathogenesis	Neuropathy Type
Vinca alkaloids	2 mg [21]	All grade: up to 96% Severe (grade 3-4): up to 37%	Single dose level, cumulative dose level	Microtubule-mediated cellular and axonal transport dysfunction	Sensory; distal lower extremities and progresses proximally.
Platinum	60 mg/m^2 [20]	30%-40%	Single dose level, cumulative dose level, infusion duration (oxaliplatin), treatment duration (oxaliplatin) Late presentation common with cisplatin	Cisplatin, Oxaliplatin (chronic): Irreversible cross-linking to DNA and neuronal apoptosis Oxaliplatin (acute): voltage-dependent sodium channel dysfunction	Cisplatin: Chronic sensory neuropathy Oxaliplatin: acute symptoms and chronic sensory neuropathy
Bortezomib and thalidomide	Bortezomib: 5th cycle dose of 30 mg/m^2 [23] Thalidomide: >200 mg/ d	Bortezomib: 37-64%, up to 33% severe Thalidomide: 23-70%, up to 13% severe	Single dose level, cumulative dose level, treatment duration	Mitochondrial dysfunction in axons; mitochondrial calcium release leading to apoptotic cascade activation	Bortezomib: Small fiber sensory neuropathy (*i.e.* c-fibers) associated with burning pain; distal lower limbs Thalidomide: sensory neuropathy – prominent paresthesia in the hands and feet along with numbness and mild motor dysfunction
Epothilones	>40 mg/ m^2 [26]	15-64%	dose per treatment cycle, duration of infusion, and cumulative dose	Microtubule dysfunction	Sensory predominant, reversible
Arsenic trioxides	10 mg/d [28]	2-42%		Acute axonal damage and demyelination	chronic sensory and motor polyneuropathy
Taxanes	175 mg/m^2 every three weeks [20]	Up to 30% as monotherapy, 70% when combined with platinum	Increased frequency and dose, as well as cumulative dosing	interfere with metabolic calcium signaling; disruption of tubulin depolymerization in axonal transport	Sensory predominant with motor deficits in severe

5.5. Arsenic Trioxides

Arsenic Trioxide (ATO) is often used in the treatment of Acute Promyelocytic Leukemia (APL). While highly effective, peripheral neuropathy is a notable side effect of ATO treatment in APL patient populations. In a recent retrospective analysis, the cumulative incidence of peripheral neuropathy was found to be 10.3% following ATO therapy [29]. The neuropathy has been characterized as both mild and reversible, but sensory and motor polyneuropathy has been observed chronically. The pathogenesis is not well understood, but findings of acute axonal damage with demyelination have been reported previously in addition to associations with thiamine deficient states [30].

5.6. Taxanes

Taxane compounds like Paclitaxel and Docetaxel have been utilized for advanced ovarian and breast cancer and are associated with DIPNvia the protein kinase C/extracellular signal-regulated kinase pathway in the spinal cord in lumbar segments 4-6 and dorsal root ganglions [31]. Increased frequency and dose, as well as cumulative dosing, increases the risk of taxane-induced DIPN, but most patients show symptom improvement or complete resolution after 6 months, with the exception of the most severe cases. The incidence of DIPN was found to be 30% when paclitaxel was administered as a single agent in the treatment of breast cancer. When used at a lower dose and in combination with carboplatin for treatment of ovarian cancer, the incidence decreased to 6%. However, the incidence of DIPN has been reported up to 70% with the addition of platinum chemotherapy to paclitaxel [1]. Although primarily a sensory neuropathy, severe cases have included motor deficits [20]. Taxane compounds interfere with metabolic calcium signaling, subsequently interfering with tubulin depolymerization in the neuronal axons. Paclitaxel has also been shown to alter sensory axon and neuroglial function within the dorsal root ganglion. Table **2** lists the characteristics of chemotherapeutic agent-related DIPN.

6. ANTIBIOTICS

6.1. Antimycobacterials

Various classes of antibiotics have been associated with peripheral neuropathy, but only the antimycobacterial agents and metronidazole are considered herein. Tuberculosis (TB) treatment requires multiple drugs for months to prevent resistance, Including Isoniazid (INH), Ethambutol (EMB),

rifampin, and pyrazinamide. Both INH and EMB are associated with DIPN, as well as linezolid, a second line drug for TB treatment.

INH is an inhibitor of mycolic acid synthesis of mycobacteria, but also interferes with human vitamin B6 synthesis, which is the suspected mechanism behind INH-induced peripheral neuropathy. According to van der Watt *et al*., the risk of developing DIPN is dose dependent, as 2-12% of patients treated with low or standard doses of isoniazid at 3-5 mg/kg/day developed DIPN, whereas 44% treated with increased doses of 16-25 mg/kg/day developed DIPN [32]. These rates are increased with concomitant HIV infection, but HIV status does not affect symptom onset. Biehl and Nimitz report that those receiving higher doses of INH (>10 mg/kg/day) were more likely to develop neuropathy complications within 3-5 weeks, while those receiving doses of 3-5 mg/kg/day were shown to develop complications after 16 weeks [33]. These complications can be reversed within weeks to months *via* supplementation with pyridoxine, and it is recommended that vitamin B6 be given concomitantly with INH.

Ethambutol inhibits mycobacterial cell wall synthesis but is associated with the serious side effect of optic neuritis. It is suspected that EMB chelates zinc, affecting mitochondrial metal-containing enzymes in retinal ganglion neurons, as demonstrated by Yoon *et al.* [34]. The usual onset of symptom is months after starting treatment and usually presents as bilateral vision loss, which is mostly reversible. However, unilateral vision loss at first has been noted, with an ultimate loss in the other eye. Moreover, Koul *et al*. report that EMB toxicity is dose dependent, in that the percentage of optic neuritis in those taking >35 mg/kg/day, 25 mg/kg/day, and 15 mg/kg/day was 18%, 6%, and <1% respectively [35].

Irreversible peripheral neuropathy has also been associated with linezolid, a bacterial protein synthesis inhibitor used to treat MRSA and multi-drug resistant TB (MDR-TB). There is some debate as to whether linezolid alone can cause DIPN since it is usually implemented after regimens of isoniazid and ethambutol. For example, in a 30-person retrospective trial regarding MDR-TB treatment, patients were treated with 600 mg linezolid, at least 3 other antibiotics, and vitamin B6. Six patients developed irreversible peripheral neuropathy, yet a correlation between linezolid and DIPN could not be made due to the MDR-TB treatment regimen [36]. However, in another study, 9 of 94 patients with osteomyelitis developed DIPN after being treated with linezolid alone or in combination with rifampin [37].

Metronidazole (MNZ), a bacterial DNA binder, used for a variety of bacterial and protozoan infections, has also been associated with DIPN. DIPN is a rare consequence of prolonged treatment with MNZ, but in a study of 13 patients with Crohn's disease treated with 15-20 mg/kg/day MNZ for months, 11 developed peripheral neuropathy, reversible upon cessation of treatment [38]. Interestingly, a case of autonomic neuropathy in a 15-year-old treated with MNZ for vaginitis has been reported, as well as an instance in which long term use caused reversible optic neuropathy [39]. (Table **3**) lists the characteristics of antibiotic-related DIPN.

7. IMMUNOSUPPRESSIVE AGENTS

Immunosuppressant drugs of various classes have been shown to cause DIPN. Biologicals like adalimumab, infliximab, and etanercept are tumor necrosis factor-α (TNF-α) inhibitors indicated for the treatment of inflammatory bowel disease, rheumatoid arthritis, and other diseases to tamper the inflammatory response. They can unfortunately induce autoimmune conditions themselves, including Guillain-Barré Syndrome (GBS), Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, and others. Shin *et al*. report that a 56-year-old with rheumatoid arthritis presented with ataxia and dysarthria after a flu-vaccine and infusion with infliximab, thereon progressing to hyporeflexia, generalized weakness, and abducens palsy after subsequent infliximab injections. The symptoms were consistent with Miller-Fisher syndrome and the diagnosis was ultimately confirmed. The patient rapidly improved after two doses of IVIG [40]. Similarly, the FDA has reported 15 patients who developed GBS roughly 4 months after starting TNF-α inhibitor therapy. Nine received infliximab, five received etanercept, and one received adalimumab. Once each drug was stopped and IVIG, plasmapheresis, or corticosteroids started,

Table 3. Characteristics of antibiotic-related DIPN.

Antibiotic	Incidence of PN	Risk Factors for PN	Pathogenesis	Type of Neuropathy
Isoniazid	2-44%	Alcohol dependence, malnutrition, diabetes, HIV, elderly and pregnant	Interference with vitamin B6 synthesis	Sensory peripheral neuropathy
Ethambutol	1-18%	increasing age, prolonged duration of EMB, a higher dose, hypertension, poor renal function, diabetes, and concurrent optic neuritis, related to tobacco and alcohol [4]	Zinc chelation affecting mitochondrial metal-containing enzymes and excitotoxic pathway	Optic neuropathy
Linezolid	13-20%	Prolonged treatment and increased doses	Unknown, could be related to protein inhibition and mitochondrial toxicity	Sensory peripheral neuropathy and optic neuropathy
Metronidazole	10-85%	Chronic treatment and increased dose	Axonal degeneration, shown to bind to neuronal RNA	Motor and Sensory peripheral neuropathy, optic and autonomic neuropathy

Table 4. Characteristics of immunosuppressant-related DIPN.

Drug Class	Incidence of PN	Risk Factors for PN	Pathogenesis	Type of Neuropathy
Biologicals	.003%	Dose and duration of drug, antecedent URI or fever-like illness, too little TNF-α	T cell and humoral immune attack on peripheral myelin [1, 9], vasculitis-induced nerve ischemia, and inhibition of axon signaling	Guillain-Barré syndrome, Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, mononeuropathy multiplex, and axonal sensorimotor polyneuropathies
Interferons	Rare	Concomitant autoimmune disease, injection site of interferon β	immune mediated myelin degradation, vessel occlusion leading to nerve ischemia, induction of anti-GM1 antibodies	Chronic inflammatory demyelinating polyneuropathy, acute axonal polyneuropathy, demyelinating polyneuropathy, vasculitic neuropathy
Leflunomide	5-10%	Older age, history of diabetes, previous use of neurotoxic drugs, alcoholism	Possibly due to drug induced neurologic vasculitis, epineural perivascular inflammation [43]	Distal axonal, sensory or sensorimotor polyneuropathy

symptoms regressed partially or completely in 12 patients, and remained in another [40]. Some patients had antecedent infections that predisposed them to developing GBS, but the involvement of biologicals in the development of symptoms cannot be ignored given the improvement once the drug was stopped.

Interferons are cytokines that inhibit T-cell proliferation, increase anti-inflammatory cytokines, and are known to decrease TNF-α. These drugs are used as therapy for a wide array of disease, with the noteworthy indications of interferon β's role against multiple sclerosis, and interferon α's application against hepatitis B and C. DIPN caused by interferons is rare, but a few cases exist in which interferon α treatment for chronic hepatitis caused both autoimmune polyradiculopathy and chronic inflammatory demyelinating polyneuropathy. Once treatment was stopped and either plasmapheresis or IVIG started, the patients' leg weakness and paresthesia improved [41, 42]. Additionally, a few reports exist regarding interferon β-induced peripheral neuropathy in patients with MS, also resolving with cessation of treatment. Additionally, focal neuropathy at interferon β injection sites for MS has been reported, specifically in the radial nerve distribution, again resolving in months after cessation [43].

A relatively new treatment for rheumatoid arthritis, Leflunomide inhibits proliferation of T cells and pyrimidine synthesis by inhibiting dihydroorotate dehydrogenase. It has also been associated with reversible peripheral neuropathy. Bharadwaj and Haroon reported peripheral neuropathy developing in 10% of patients treated with leflunomide. Those who experienced neuropathy reported paresthesia, confirmed by nerve conduction studies, about 3 months after starting the drug, and stopping the drug reversed the symptoms [44]. Similarly, a case report of 14 instances of leflunomide-induced neuropathy noted that, although some patients were on other neurotoxic drugs, had a history of diabetes, a previous diagnosis of neuropathy, or other risk factors for neuropathy, their neuropathy worsened while on leflunomide or improved once the drug was stopped [45]. DIPN is possible with the treatment of leflunomide, but other contributing factors warrant close monitoring, especially when starting treatment [46]. Table **4** lists the characteristics of immunosuppressant-related DIPN.

8. NRTIs

NRTIs associated with peripheral neuropathy include zalcitabine (ddC), didanosine (ddI), stavudine (d4T), and lamivudine. The incidence of peripheral neuropathy with these drugs varies by agent and is a frequent reason cited for discontinuation of antiretroviral therapy. Up to 10% of patients taking zalcitabine have been reported to stop treatment due to this side effect [47]. 34% of patients treated with didanosine develop painful peripheral neuropathy [48], and 1-2% stop therapy as a result [47]. In patients treated with stavudine, 49.8% of patients taking 40 mg b.i.d. developed peripheral neuropathy, and 11.2% taking less than 30 mg b.i.d. developed peripheral neuropathy [48]. Lamivudine seems to have a low incidence of peripheral neuropathy compared to other NRTIs, although the reason for this is unclear [49].

Patient-associated risk factors for NRTI-induced peripheral neuropathy include prior underlying neuropathy [50], prior HIV-associated neuropathy, underlying malignancy [51], and low CD4 count or immunodeficiency as shown in Table **5**. Specifically, $CD4^+$ T lymphocyte count <50 cells/mm^3 was strongly associated with an increased risk of NRTI-induced peripheral neuropathy [48]. Risk of painful NRTI-associated peripheral neuropathy also varies with dose and treatment regimen: higher doses of NRTIS [51, 52], as well as combination therapy both, seem to be associated with increased incidence of peripheral neuropathy [49]. Additionally, genetic or age-related metabolic impairments may exacerbate side effects due to reduced drug clearance [49]. Alcohol use is common in patients taking NRTIs and has been associated with worse peripheral neuropathy due to the enhanced ddC effect on mitochondrial DNA damage [53].

The pathophysiology of peripheral neuropathy due to NRTIs is not entirely understood; however, it is thought to be primarily due to inhibition of γ-DNA polymerase, which

Table 5. Peripheral neuropathy with nucleoside reverse transcriptase inhibitors.

Agent Group	Incidence	Dose	Risk Factors	Pathogenesis	Type of Neuropathy
NRTIs	Zalcitabine: 30-100% Didanosine: 23% Stavudine: 31% Lamivudine: rare	Zalcitabine 2.25 mg/day Didanosine: 400 mg/day Stavudine: 30-40 mg b.i.d. Lamivudine: 300 mg/day	Prior neuropathy Underlying malignancy Low CD4 count High dose Combination therapy Metabolic impairments Alcohol use	Inhibition of γ-DNA polymerase leading to mitochondrial dysfunction	Distal axonal-type sensory neuropathy

is responsible for replication of mitochondrial DNA. This leads to mitochondrial dysfunction, accumulation of toxic metabolites, and increased lactate production [51]. The neuropathy associated with NRTI use is primarily peripheral, likely due to the fact that peripheral nerves have a leakier blood-nerve barrier compared to central neurons [51], possibly making them more susceptible than central neurons to damage by NRTIs. NRTIs cause a distal axonal-type sensory neuropathy that can be similar to and difficult to distinguish from primary HIV-induced neuropathy [51]. It often manifests clinically as burning, shooting pain, distal weakness, and a decreased ankle jerk reflex [47]. Electrophysiology studies on patients with NRTI-induced peripheral neuropathy show a decreased action potential amplitude with a normal latency, which is a pattern commonly seen in sensory axonal degeneration [49].

9. OTHER AGENTS

9.1. Levodopa

Peripheral neuropathy as a side effect of levodopa therapy in patients with Parkinson's disease has been shown to occur in as many as 55% of patients taking levodopa [54], and at least 20% of patients with cumulative exposure greater than three years as shown in Table **6** [55].

The risk of developing peripheral neuropathy increases with higher doses, and this risk is particularly high at doses higher than 1500 mg/day [56]. Ceravolo *et al.* showed that the average dose in patients not reporting neuropathy was 400 mg/day, while the average dose in patients reporting neuropathy was 700 mg/day [57]. Higher blood concentrations of Homocysteine (HCY), and lower levels of vitamin B12 [55] are also associated with an increased risk of peripheral neuropathy. Route of administration affects the incidence of peripheral neuropathy: Levodopa-Carbidopa Intestinal Gel Infusion (LCIG) facilitates higher drug levels compared to oral treatment [56]. A lower BMI seems to correlate with a higher incidence of peripheral neuropathy [56]. Some studies have also suggested that variations in methyl tetrahydrofolate reductase could predispose some patients to the development of peripheral neuropathy [57].

The pathophysiology of levodopa-induced neuropathy seems to be mediated by accumulation of serum homocysteine, cobalamin-related metabolites, and methylmalonic acid and a decrease in the levels of vitamin B12 [55]. Conversion of levodopa to dopamine requires a methyl group from S-adenosylmethionine, leading to Hcy formation. Remethylation of Hcy requires vitamin B12, reducing vitamin B12 levels and increasing Hcy. In animal studies, levodopa intake was shown to increase serum Hcy concentration [54] and free radical accumulation [58].

The peripheral neuropathy seen with levodopa treatment is an axonal-type sensory peripheral neuropathy that tends to be mildly symptomatic or even asymptomatic in some cases [54]. On nerve conduction studies, a reduction in sural nerve amplitude has been noted [57].

9.2. Azoles

The reported incidence of peripheral neuropathy in patients treated with azoles is highly varied in the literature. The manufacturer's data sheets for the triazole drugs list peripheral neuropathy as a rare side effect; however, Boussaud *et al*. report an incidence of 30% (n=8) in transplant patients taking voriconazole [59], and Baxter *et al*. report incidence rates of 9% and 17% in patients treated with voriconazole and itraconazole, respectively [60].

The risk of peripheral neuropathy associated with azole therapy seems to be higher in patients with diabetes mellitus, perhaps due to the predisposition to neuropathies in this population [61]. An increased risk of neuropathy has been associated with higher doses of azoles, from 150-350 mg. b.i.d. [59, 60]; however, other studies have shown peripheral neuropathy even when patients are within the therapeutic window [60].

The pathophysiology of azole-induced peripheral neuropathy is unclear. The azole group has been theorized to play a role in the development of peripheral neuropathy; however, many other drugs that have not been shown to induce peripheral neuropathy include azole groups [60]. Chen *et al.* suggested a mitochondrial-dependent mechanism [62], and mitochondrial destruction has been implicated in other drug-induced neuropathies. A possible predisposition may be the wide variety of genetic polymorphisms in the CYP2C19 system, which metabolizes voriconazole, resulting in a wide range of serum concentrations [63]. Cartwright *et al.* have observed excess accumulation of phospholipids in canine neurons treated with azoles; however, this has not been shown to cause peripheral neuropathy in humans [64].

Symptoms of azole-induced peripheral neuropathy include tingling and numbness that resolve after discontinuation of therapy [60], decreased position and vibratory sensa-

Table 6. Peripheral neuropathy with other agents.

Agent Group	Incidence	Dose	Risk Factors	Pathogenesis	Type of Neuropathy
Levodopa	20-55%	Average in patients without neuropathy: 400 mg/day Average dose in patients with neuropathy: 700 mg/day Highest risk at doses > 1500 mg/day	High dose treatment High serum Hcy Low vitamin B12 LCIG administration Low BMI	Accumulation of serum homocysteine and cobalamin-related metabolites, free radical accumulation	Axonal-type sensory peripheral neuropathy
Triazole	9-30%	150-350 mg. b.i.d.	Diabetes mellitus High dose treatment	Unclear: possibly mitochondrial-dependent	Small fiber axonal-type, predominantly sensory neuropathy, symmetrical

tion, and abnormal EMG [61]. The neuropathy is sensory-predominant, axonal, and typically symmetrical, with small fibers affected the earliest [60, 65].

10. TREATMENT

Most commonly, DIPN presents with only mild sensory paraesthesias and does not warrant any specific intervention other than a possible reduction or cessation of the specific agent causing neuropathy [1]. However, when the neuropathy causes significant disability or pain several treatment options are available to help reduce the DIPN and subsequent pain. Current management includes Tricyclic Antidepressants (TCAs), serotonin and noradrenalin reuptake inhibitors (SSRIs and SNRIs), gabapentinoids, and other interventional modalities.

While the exact mechanism of TCAs analgesic effects has not been fully elicited, it is thought to act by activating the descending inhibitory pain pathway. TCAs exert analgesic effects at lower doses than typically needed for antidepressant action, and *via* a mechanism independent of their antidepressant effects [66]. TCAs are well studied, with much evidence to support their use in randomized placebo-controlled studies which evaluated amitriptyline and nortriptyline in the treatment of neuropathic pain. TCAs should be started at low doses (10-25mg) and slowly titrated up to analgesic effects primarily due to concerns for adverse anticholinergic effects [67]. While the risk profile for TCAs is relatively low, precautions should be used in patients with comorbidities such as heart disease, glaucoma, and prostatic hyperplasia. Dry mouth and constipation are common side effects but are rarely seen in the low doses used for neuropathic pain.

Gabapentinoids such as gabapentin and pregabalin have also proven efficacious in the treatment of neuropathic pain. Structurally similar to GABA, each bind to the $\alpha 2\delta$ subunit of voltage-dependent calcium channel [67]. Their analgesic effect occurs by suppression of the presynaptic calcium influx required for the release of excitatory neurotransmitters. Gabapentinoids exhibit a low-risk profile, and common adverse effects include dizziness, lightheadedness, sedation, and edema. Dosage for gabapentin commonly begins at 150mg twice daily and can be titrated up to 300 mg b.i.d.

Duloxetine is a selective noradrenalin reuptake inhibitor commonly used in the treatment of depression and may also be used for analgesia in the treatment of neuropathic pain. Like TCAs, duloxetine activates the descending pain inhibitory system by increasing the availability of serotonin and noradrenalin in the synaptic cleft. Duloxetine is generally well tolerated; common adverse reactions include somnolence, nausea, and constipation [67]. Given Duloxetine's lower risk profile, it is sometimes preferred over TCAs for neuropathic pain.

The pain inflicted by DIPN is often refractory to pharmacologic non-interventional therapies. In this setting, interventional therapies can offer patients some relief. A recent literature review examined neural blockade, Spinal Cord Stimulation (SCS), intrathecal medication, and neurosurgical interventions for neuropathic pain [68]. Due to the lack of quality clinical trials, the authors were unable to provide strong recommendations for interventional therapies in the treatment of neuropathic pain. Interventional therapies should be withheld until the patient has failed pharmacologic, non-interventional therapies.

Aside from the pharmacologic interventions discussed above, recent evidence has emerged regarding the use of vitamins and other alternative therapies in the treatment of neuropathy. Several studies indicate that these alternative medicines may offer significant benefit to patients suffering from peripheral neuropathy and neuropathic pain. Alpha-Lipoic Acid (ALA), acetyl-L-carnitine, benfotiamine, methylcobalamin, gamma-linolenic acid, magnesium, and topical capsaicin have exhibited considerable impact in reducing neuropathic symptoms [69]. Of note, these studies have not explored directly their role in DIPN. Rather, they have exhibited efficacy in other common causes of neuropathy, as supplementation to alternative therapies resulted in significant improvements in diabetic neuropathy. One study investigated the addition of a supplement containing L-methylfolate, pyridoxal 5-phosphate, and methylcobalamin to other medications (*e.g.*, pregabalin, gabapentin, or duloxetine) with a resultant 26% decrease in pain symptoms compared to 15% for those taking the medication alone [70]. Encouragingly, these adjuvants accomplished significant reductions in pain symptoms without incurring any significant adverse effects.

Lastly, it is worth mentioning some exciting developments for the prophylaxis of DIPN in certain classes of chemotherapeutic compounds. The neuropathic side effects of bortezomib and taxanes, in particular, have been limited by concomitant administration of tamoxifen, a protein kinase C inhibitor [31].

CONCLUSION

Drug-induced peripheral neuropathy is a common and painful condition caused by many different and frequently prescribed medications. Most often, DIPN is seen in chemotherapeutic agents, antimicrobials, cardiovascular drugs, psychotropic, and anticonvulsant drugs. While certain drugs exhibit more consistent neuropathic side effects, such as the chemotherapeutic compounds, others are more commonly prescribed by a larger proportion of providers, such as the statins. As such, awareness of these drugs' potential for adverse neuropathic effect is important for providers caring for patients receiving said drugs who report new onset symptoms of pain, paresthesia, or weakness. DIPN is more likely to occur in patients with concomitant risk factors such as preexisting neuropathy, diabetes, and associated genetically predisposing diseases. Prevention of DIPN is especially important because treatment often proves challenging. While many pharmacologic therapies have demonstrated analgesic potential in the pain caused by DIPN, many patients remain refractive to treatment. More studies are needed to elucidate the effectiveness of interventional, neuromodulating therapies.

LIST OF ABBREVIATIONS

ALA	=	Alpha-lipoic Acid
APL	=	Acute Promyelocytic Leukemia
ATF3	=	Activating Transcription Factor 3
ATO	=	Arsenic Trioxide
DIPN	=	Drug-induced Peripheral Neuropathy
DRG	=	Dorsal Root Ganglion
EMB	=	Ethambutol
HCY	=	Homocysteine
INH	=	Isoniazid
LCIG	=	Levodopa-carbidopa Intestinal Gel infusion
MNZ	=	Metronidazole
MS	=	Multiple Sclerosis
NRTI	=	Nucleoside Reverse Transcriptase Inhibitors
SCS	=	Spinal Cord Stimulation
SSRIs and SNRIs	=	Serotonin and Noradrenalin Reuptake Inhibitor
TCA	=	Tricyclic Antidepressant
TNF-α	=	Tumor Necrosis Factor-α

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Vilholm OJ, Christensen AA, Zedan AH, Itani M. Drug-induced peripheral neuropathy. Basic Clin Pharmacol Toxicol 2014; 115(2): 185-92. http://dx.doi.org/10.1111/bcpt.12261

[2] Green S, Holton A. Drug-induced peripheral neuropathy. Adverse Drug React Bull 2016; 300(1): 1159-62. http://dx.doi.org/10.1097/FAD.0000000000000020

[3] Ma J, Kavelaars A, Dougherty PM, Heijnen CJ. Beyond symptomatic relief for chemotherapy-induced peripheral neuropathy: Targeting the source. Cancer Wiley-Blackwell; 2018 Jun; 124(11): 2289-98.

[4] Cashman CR, Höke A. Mechanisms of distal axonal degeneration in peripheral neuropathies. Neurosci Lett 2015; 596: 33-50. http://dx.doi.org/10.1016/j.neulet.2015.01.048 PMID: 25617478

[5] McDonald ES, Randon KR, Knight A, Windebank AJ. Cisplatin preferentially binds to DNA in dorsal root ganglion neurons *in vitro* and *in vivo*: A potential mechanism for neurotoxicity. Neurobiol Dis 2005; 18(2): 305-13. http://dx.doi.org/10.1016/j.nbd.2004.09.013 PMID: 15686959

[6] Kidd JF, Pilkington MF, Schell MJ, *et al.* Paclitaxel affects cytosolic calcium signals by opening the mitochondrial permeability transition pore. J Biol Chem 2002; 277(8): 6504-10. http://dx.doi.org/10.1074/jbc.M106802200 PMID: 11724773

[7] Apostolski S, McAlarney T, Hays AP, Latov N. Complement dependent cytotoxicity of sensory ganglion neurons mediated by the gp120 glycoprotein of HIV-1. Immunol Invest 1994; 23(1): 47-52. http://dx.doi.org/10.3109/08820139409063432 PMID: 8144198

[8] Meregalli C, Chiorazzi A, Carozzi VA, *et al.* Evaluation of tubulin polymerization and chronic inhibition of proteasome as citotoxicity mechanisms in bortezomib-induced peripheral neuropathy. Cell Cycle 2014; 13(4): 612-21. http://dx.doi.org/10.4161/cc.27476 PMID: 24335344

[9] Adelsberger H, Quasthoff S, Grosskreutz J, Lepier A, Eckel F, Lersch C. The chemotherapeutic oxaliplatin alters voltage-gated Na(+) channel kinetics on rat sensory neurons. Eur J Pharmacol 2000; 406(1): 25-32. http://dx.doi.org/10.1016/S0014-2999(00)00667-1 PMID: 11011028

[10] Nagle S, Strelec LE, Loren AW, *et al.* Brentuximab-induced peripheral neuropathy: Risk factors and patient experiences. J Clin Oncol 2017 Feb; 35(5-suppl): 120-0.

[11] Bao T, Basal C, Seluzicki C, Li SQ, Seidman AD, Mao JJ. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: Prevalence, risk factors, and fall risk. Breast Cancer Res Treat 2016; 159(2): 327-33. http://dx.doi.org/10.1007/s10549-016-3939-0 PMID: 27510185

[12] Hur J, Guo AY, Loh WY, Feldman EL, Bai JPF. Integrated systems pharmacology analysis of clinical drug-induced peripheral neuropathy. CPT pharmacometrics syst pharmacol Wiley-Blackwell; 2014 May; 3(5)e114. http://dx.doi.org/10.1038/psp.2014.11

[13] Wu C, Tcherny-Lessenot S, Dai W, *et al.* Assessing the risk for peripheral neuropathy in patients treated with dronedarone compared with that in other antiarrhythmics. Clin Ther 2018; 40(3): 450-455. http://dx.doi.org/10.1016/j.clinthera.2018.01.015 PMID: 29500139

[14] Niimi N, Yako H, Tsukamoto M, *et al.* Involvement of oxidative stress and impaired lysosomal degradation in amiodarone-induced schwannopathy. Eur J Neurosci. Wiley/Blackwell (10.1111); 2016; 44: pp. (1)1723-33. http://dx.doi.org/10.1111/ejn.13268

[15] West B, Williams CM, Jilbert E, James AM, Haines TP. Statin use and peripheral sensory perception: a pilot study. Somatosens Mot Res 2014; 31(2): 57-61. http://dx.doi.org/10.3109/08990220.2013.840281 PMID: 24219409

[16] Svendsen T de K, Nørregaard HP, García RLA, *et al.* Statins and polyneuropathy revisited: Case-control study in Denmark, 1999-2013. Br J Clin Pharmacol Wiley-Blackwell; 2017; 83(9): 2087-95.

[17] Gaist D, Jeppesen U, Andersen M, García Rodríguez LA, Hallas J, Sindrup SH. Statins and risk of polyneuropathy: A case-control study. Neurology 2002; 58(9): 1333-7.

http://dx.doi.org/10.1212/WNL.58.9.1333 PMID: 12011277

[18] Bhalla S, Singh N, Jaggi AS. Statins: Do they aggravate or ameliorate neuropathic pain? J Pain 2014; 15(11): 1069-80.

[19] Gürkov R. Amiodarone: A newly discovered association with bilateral vestibulopathy. Front Neurol 2018; 6(9): 119. http://dx.doi.org/10.3389/fneur.2018.00119

[20] Brewer JR, Morrison G, Dolan ME, Fleming GF. Chemotherapy-induced peripheral neuropathy: Current status and progress. Gynecol Oncol 2016; 140(1): 176-83. http://dx.doi.org/10.1016/j.ygyno.2015.11.011 PMID: 26556766

[21] Mora E, Smith EML, Donohoe C, Hertz DL. Vincristine-induced peripheral neuropathy in pediatric cancer patients. Am J Cancer Res e-Century Publishing Corporation 2016; 6(11): 2416-30.

[22] Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. Ann Neurol 2017; 81(6): 772-81. http://dx.doi.org/10.1002/ana.24951 PMID: 28486769

[23] Fujita S, Hirota T, Sakiyama R, Baba M, Ieiri I. Identification of drug transporters contributing to oxaliplatin-induced peripheral neuropathy. J Neurochem 2019; 148(3): 373-85.

[24] Delforge M, Bladé J, Dimopoulos MA, *et al.* Treatment-related peripheral neuropathy in multiple myeloma: The challenge continues. Lancet Oncol 2010; 11(11): 1086-95. http://dx.doi.org/10.1016/S1470-2045(10)70068-1 PMID: 20932799

[25] Luo J, Gagne JJ, Landon J, Avorn J, Kesselheim AS. Comparative effectiveness and safety of thalidomide and lenalidomide in patients with multiple myeloma in the United States of America: A population-based cohort study. Eur J Cancer 2017; 70: 22-33. http://dx.doi.org/10.1016/j.ejca.2016.10.018 PMID: 27866096

[26] Ludwig H, Delforge M, Facon T, *et al.* Prevention and management of adverse events of novel agents in multiple myeloma: A consensus of the European myeloma network. Leukemia 2018; 32(7): 1542-60. http://dx.doi.org/10.1038/s41375-018-0040-1 PMID: 29720735

[27] Yin Y, Qi X, Qiao Y, *et al.* The association of neuronal stress with activating transcrip-tion factor 3 in dorsal root ganglion of *in vivo* and *in vitro* models of bortezomib-induced neuropathy. Curr Cancer Drug Targets [Internet] 2018. Available from: http: //www.ncbi.nlm.nih.gov/ pubmed/30289077 [Accessed 13 Dec 2018].

[28] Vahdat LT, Thomas ES, Roché HH, *et al.* Ixabepilone-associated peripheral neuropathy: Data from across the phase II and III clinical trials Support Care Cancer Springer-Verlag 2012; Nov 20(11): 2661-8. http://dx.doi.org/10.1007/s00520-012-1384-0

[29] Kim PG, Bridgham K, Chen EC, *et al.* Incident adverse events following therapy for acute promyelocytic leukemia. Leuk Res Rep 2018; 9: 79-83. http://dx.doi.org/10.1016/j.lrr.2018.05.001 PMID: 29892554

[30] Kühn M, Sammartin K, Nabergoj M, Vianello F. Severe acute axonal neuropathy following treatment with arsenic trioxide for acute promyelocytic leukemia: A case report. Mediterr J Hematol Infect Dis 2016; 8(1): e2016023. http://dx.doi.org/10.4084/mjhid.2016.023 PMID: 27158436

[31] Tsubaki M, Takeda T, Matsumoto M, *et al.* Tolerability of prolonged linezolid therapy in bone and joint infection: protective effect of rifampicin on the occurrence of anaemia? J Antimicrob Chemother Oxford University Press; 2018 Oct; 65(10): 2224-30.http: //www.ncbi.nlm.nih.gov/pubmed/30360692

[32] van der Watt JJ, Harrison TB, Benatar M, Heckmann JM. Polyneuropathy, anti-tuberculosis treatment and the role of pyridoxine in the HIV/AIDS era: A systematic review. Int J Tuberc Lung Dis 2011; 15(6): 722-8. http://dx.doi.org/10.5588/ijtld.10.0284 PMID: 21477422

[33] Biehl JP, Nimitz HJ. Studies on the use of high dose of isoniazid. I. Toxicity studies. Am Rev Tuberc 1954; 70(3): 430-41. PMID: 13189058

[34] Yoon YH, Jung KH, Sadun AA, Shin H-C, Koh J-Y. Ethambutol-induced vacuolar changes and neuronal loss in rat retinal cell culture: mediation by endogenous zinc. Toxicol Appl Pharmacol Academic Press 2000 Jan; 162(2): 107-4.

[35] Koul PA. Ocular toxicity with ethambutol therapy: Timely recaution. Lung India. Wolters Kluwer - Medknow Publications; 2015; 32(1): 1-3.

[36] Schecter GF, Scott C, True L, Raftery A, Flood J, Mase S. Linezolid in the treatment of multidrug-resistant tuberculosis. Clin Infect Dis 2010; 50(1): 49-55. http://dx.doi.org/10.1086/648675

[37] Legout L, Valette M, Dezeque H, *et al.* Tolerability of prolonged linezolid therapy in bone and joint infection: protective effect of rifampicin on the occurrence of anaemia? J Antimicrob Chemother 2010; 65(10): 2224-30.

[38] Duffy LF, Daum F, Fisher SE, *et al.* Peripheral neuropathy in Crohn's disease patients treated with metronidazole. Gastroenterology 1985; 88(3): 681-4. http://dx.doi.org/10.1016/0016-5085(85)90137-4 PMID: 2981752

[39] Hobson-Webb LD, Roach ES, Donofrio PD. Metronidazole: Newly recognized cause of autonomic neuropathy. J Child Neurol 2006; 21(5): 429-31. http://dx.doi.org/10.1177/08830738060210051201 PMID: 16901452

[40] Shin I-SJ, Baer AN, Kwon HJ, Papadopoulos EJ, Siegel JN. Guillain-Barré and Miller Fisher syndromes occurring with tumor necrosis factor α antagonist therapy. Arthritis Rheum 2006; 54(5): 1429-34. http://dx.doi.org/10.1002/art.21814 PMID: 16645971

[41] Marzo ME, Tintoré M, Fabregues O, Montalbán X, Codina A. Chronic inflammatory demyelinating polyneuropathy during treatment with interferon-alpha. J Neurol Neurosurg Psychiatry. BMJ Publishing Group Ltd 1998; 65: p. (4)604.

[42] Kato-Motozaki Y, Komai K, Takahashi K, *et al.* Polyethylene glycol interferon α-2b-induced immune-mediated polyradiculoneuropathy. Internal Medicine 2009; 48(7): 569-72.

[43] Créange A, Lefaucheur JP. Focal neuropathy associated with cutaneous necrosis at the site of interferon-beta injection for multiple sclerosis. J Neurol Neurosurg Psychiatry 2000; 68(3): 395.

[44] Bharadwaj A, Haroon N. Peripheral neuropathy in patients on leflunomide. Rheumatology. 2004; 43(7): 934-4. http://dx.doi.org/10.1093/rheumatology/keh191

[45] Martin K, Bentaberry F, Dumoulin C, *et al.* Neuropathy associated with leflunomide: A case series. Ann Rheum Dis. 2005; 64(4): 649-50. http://dx.doi.org/10.1136/ard.2004.027193

[46] Carulli MT, Davies UM. Peripheral neuropathy: An unwanted effect of leflunomide? Rheumatology 2002; 41(8): 952-3. http://dx.doi.org/10.1093/rheumatology/41.8.952

[47] Pratt RW, Weimer LH. Medication and toxin-induced peripheral neuropathy. Semin Neurol 2005; 25(2): 204-16. http://dx.doi.org/10.1055/s-2005-871329 PMID: 15937736

[48] Lichtenstein KA, Armon C, Baron A, *et al.* Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV outpatient study cohort. Clin Infect Dis 2005.

[49] Abers MS, Shandera WX, Kass JS. Neurological and psychiatric adverse effects of antiretroviral drugs. CNS Drugs 2014; 28(2): 131-45. http://dx.doi.org/10.1007/s40263-013-0132-4 PMID: 24362768

[50] Chaudhry V, Chaudhry M, Crawford TO, Simmons-O'Brien E, Griffin JW. Toxic neuropathy in patients with pre-existing neuropathy. Neurology 2003; 60(2): 337-40. http://dx.doi.org/10.1212/01.WNL.0000043691.53710.53 PMID: 12552058

[51] Weimer LH. Medication-induced peripheral neuropathy. Curr Neurol Neurosci Rep 2003; 3(1): 86-92. http://dx.doi.org/10.1007/s11910-003-0043-8 PMID: 12507417

[52] Moreno S, Hernández B, Dronda F. Didanosine enteric-coated capsule: Current role in patients with HIV-1 infection. Drugs 2007; 67(10): 1441-62. http://dx.doi.org/10.2165/00003495-200767100-00006 PMID: 17600392

[53] Ferrari LF, Levine JD. Alcohol consumption enhances antiretroviral painful peripheral neuropathy by mitochondrial mechanisms. Eur J Neurosci 2010; 32(5): 811-8. http://dx.doi.org/10.1111/j.1460-9568.2010.07355.x PMID: 20726883

[54] Toth C, Breithaupt K, Ge S, *et al.* Levodopa, methylmalonic acid, and neuropathy in idiopathic Parkinson disease. Ann Neurol 2010; 68(1): 28-36. http://dx.doi.org/10.1002/ana.22021 PMID: 20582991

[55] Cossu G, Ceravolo R, Zibetti M, *et al.* Levodopa and neuropathy risk in patients with Parkinson disease: Effect of COMT inhibition. Park Relat Disord. 2016; 27: 81-4.

[56] Merola A, Romagnolo A, Zibetti M, Bernardini A, Cocito D, Lopiano L. Peripheral neuropathy associated with levodopa-carbidopa intestinal infusion: A long-term prospective assessment. Eur J Neurol 2016; 23(3): 501-9. http://dx.doi.org/10.1111/ene.12846 PMID: 26498913

[57] Ceravolo R, Cossu G, Bandettini di Poggio M, *et al.* Neuropathy and levodopa in Parkinson's disease: Evidence from a multicenter study. Mov Disord 2013; 28(10): 1391-7. http://dx.doi.org/10.1002/mds.25585 PMID: 23836370

[58] Gorgone G, Currò M, Ferlazzo N, *et al.* Coenzyme Q10, hyperhomocysteinemia and MTHFR C677T polymorphism in levodopa-treated Parkinson's disease patients. Neuromolecular Med 2012; 14(1): 84-90. http://dx.doi.org/10.1007/s12017-012-8174-1 PMID: 22354693

[59] Boussaud V, Daudet N, Billaud EM, *et al.* Neuromuscular Painful Disorders: A rare side effect of voriconazole in lung transplant patients under tacrolimus. J Hear Lung Transplant 2008; 27(2): 229-32.

[60] Baxter CG, Marshall A, Roberts M, Felton TW, Denning DW. Peripheral neuropathy in patients on long-term triazole antifungal therapy. J Antimicrob Chemother 2011; 66(9): 2136-9. http://dx.doi.org/10.1093/jac/dkr233 PMID: 21685202

[61] Tsiodras S, Zafiropoulou R, Kanta E, Demponeras C, Karandreas N, Manesis EK. Painful peripheral neuropathy associated with voriconazole use. Arch Neurol 2005; 62(1): 144-6. http://dx.doi.org/10.1001/archneur.62.1.144 PMID: 15642862

[62] Chen H, Chan DC. Critical dependence of neurons on mitochondrial dynamics. Curr Opin Cell Biol 2006; 18(4): 453-9. http://dx.doi.org/10.1016/j.ceb.2006.06.004 PMID: 16781135

[63] Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. Clin Pharmacokinet 2006; 45(7): 649-63. http://dx.doi.org/10.2165/00003088-200645070-00002 PMID: 16802848

[64] Cartwright ME, Petruska J, Arezzo J, *et al.* Phospholipidosis in neurons caused by posaconazole, without evidence for functional neurologic effects. Toxicol Pathol 2009; 37(7): 902-10. http://dx.doi.org/10.1177/0192623309348521 PMID: 19833913

[65] Aksoy F, Akdogan E, Aydin K, *et al.* Voriconazole-induced neuropathy. Chemotherapy 2008; 54(3): 224-7. http://dx.doi.org/10.1159/000140466 PMID: 18560230

[66] Dworkin RH, Corbin AE, Young JP Jr, *et al.* Pregabalin for the treatment of postherpetic neuralgia: A randomized, placebo-controlled trial. Neurology 2003; 60(8): 1274-83. http://dx.doi.org/10.1212/01.WNL.0000055433.55136.55 PMID: 12707429

[67] Nishikawa N, Nomoto M. Management of neuropathic pain. J Gen Fam Med . Wiley-Blackwell 2017; 18: pp. (2)56-60.

[68] Dworkin RH, O'Connor AB, Kent J, *et al.* International association for the study of pain neuropathic pain special interest group. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 2013; 154(11): 2249-61. http://dx.doi.org/10.1016/j.pain.2013.06.004 PMID: 23748119

[69] Head KA. Peripheral neuropathy: Pathogenic mechanisms and alternative therapies. Altern Med Rev 2006; 11(4): 294-329. PMID: 17176168

[70] Fonseca VA, Lavery LA, Thethi TK, *et al.* Metanx in type 2 diabetes with peripheral neuropathy: A randomized trial. Am J Med 2013; 126(2): 141-9. http://dx.doi.org/10.1016/j.amjmed.2012.06.022 PMID: 23218892