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**Burgess, J, Ferdousi, M, Gosal, D, Boon, C, Matsumoto, K, Marshall, A, Mak, T, Marshall, A, Frank, B, Malik, RA and Alam, U**

**Chemotherapy-Induced Peripheral Neuropathy: Epidemiology, Pathomechanisms and Treatment**

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### Article

**Citation** (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

**Burgess, J, Ferdousi, M, Gosal, D, Boon, C, Matsumoto, K, Marshall, A, Mak, T, Marshall, A, Frank, B, Malik, RA and Alam, U (2021) Chemotherapy-Induced Peripheral Neuropathy: Epidemiology, Pathomechanisms and Treatment. *Oncology and Therapy*. 9 (2). pp. 385-450. ISSN 2366-1070**

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# Chemotherapy-Induced Peripheral Neuropathy: Epidemiology, Pathomechanisms and Treatment

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Received: June 14, 2021 / Accepted: August 12, 2021  
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## ABSTRACT

**Purpose:** This review provides an update on the current clinical, epidemiological and pathophysiological evidence alongside the diagnostic, prevention and treatment approach to

chemotherapy-induced peripheral neuropathy (CIPN).

**Findings:** The incidence of cancer and long-term survival after treatment is increasing. CIPN affects sensory, motor and autonomic nerves and is one of the most common adverse events caused by chemotherapeutic agents, which in severe cases leads to dose reduction or

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treatment cessation, with increased mortality. The primary classes of chemotherapeutic agents associated with CIPN are platinum-based drugs, taxanes, vinca alkaloids, bortezomib and thalidomide. Platinum agents are the most neurotoxic, with oxaliplatin causing the highest prevalence of CIPN. CIPN can progress from acute to chronic, may deteriorate even after treatment cessation (a phenomenon known as coasting) or only partially attenuate. Different chemotherapeutic agents share both similarities and key differences in pathophysiology and clinical presentation. The diagnosis of CIPN relies heavily on identifying symptoms, with limited objective diagnostic approaches targeting the class of affected nerve fibres. Studies have consistently failed to identify at-risk cohorts, and there are no proven strategies or interventions to prevent or limit the development of CIPN. Furthermore, multiple treatments developed to relieve symptoms and to modify the underlying disease in CIPN have failed.

**Implications:** The increasing prevalence of CIPN demands an objective approach to identify at-risk patients in order to prevent or limit progression and effectively alleviate the symptoms associated with CIPN. An evidence base for novel targets and both pharmacological and non-pharmacological treatments is beginning to emerge and has been recognised recently in publications by the American Society of Clinical Oncology and analgesic trial design expert groups such as ACTTION.

**Keywords:** Chemotherapy; Epidemiology; Mechanism of action; Neuropathy; Neurotoxicity; Oxaliplatin; Paclitaxel; Pain; Peripheral neuropathy; Prevalence

### Key Summary Points

Chemotherapy-induced peripheral neuropathy is a common adverse event which affects the sensory, motor and autonomic nerves.

The diagnosis of chemotherapy-induced peripheral neuropathy lacks a gold standard.

There are currently no proven strategies or interventions to prevent or limit the development of chemotherapy-induced peripheral neuropathy.

A mechanistic approach is needed to address strategies for prevention and treatment of chemotherapy-induced peripheral neuropathy.

## INTRODUCTION

The most recent estimation for all-cause cancer incidence is 18.1 million new cases per year [1]. With more effective targeted cancer treatments, long-term cancer survival is increasing in high-income countries [2], as evidenced by the 27% drop in the overall cancer death rate in the United States between 1991 and 2016 [3, 4]. However, chemotherapy-induced peripheral neuropathy (CIPN) is a common and challenging complication of several frequently administered antineoplastic agents [5]. The development of CIPN may result in prolonged infusion times, dose reduction or premature cessation of chemotherapy [6–8], which may negatively impact both treatment efficacy and patient survival [9, 10]. A meta-analysis of randomised controlled trials and cohort studies showed that around half of all patients develop CIPN during treatment [10].

There is currently no gold standard for the assessment of CIPN, with a variety of clinical tools utilised in studies with heterogeneous primary outcome measures [11–21]. Indeed, subclinical nerve damage and motor involvement are poorly defined when using current standardised clinical instruments [15]. Accurate comparisons of the prevalence, incidence, prevention and treatment of CIPN are therefore problematic (Table 1). Additionally, there are considerable disparities in patient- and clinician-reported neurotoxicity. For example, in the

ICON7 trial, clinicians reported CIPN in 28% of patients, while 67% of patients reported 'quite a bit' or 'very much' tingling or numbness, with poor agreement between patients and clinicians ( $\kappa = 0.236$ , 95% confidence interval, 0.177–0.296,  $p < 0.001$ ) [22].

Chemotherapeutic agents result in neurotoxicity through a variety of mechanisms, culminating in a predominantly symmetrical sensory or sensorimotor, length-dependent neuropathy and autonomic dysfunction [23–28]. Neuropathic syndromes specific to chemotherapeutic agents can be observed, each with their own presentation and natural history [29–33] (Table 2). CIPN can develop, or continue to worsen, several months after treatment has stopped, in a phenomenon termed "coasting". The prevalence of CIPN one month after finishing chemotherapy approaches 68%, and persists in approximately one third of patients beyond 6 months [10]. Risk factors for CIPN include the agent used, cumulative dose, number of cycles, treatment duration, combination therapies, genetic predisposition, age, existing nerve damage, severity of acute symptoms and chronic alcohol consumption amongst others [15]. The ageing population and more efficacious chemotherapeutic regimens will continue to increase cancer cure rates and long-term cancer survival [34], together with CIPN [35]. It is therefore imperative to develop effective strategies for the early identification with prevention and more efficacious management of CIPN.

## LITERATURE SEARCH METHODOLOGY

Electronic database searches were undertaken in EMBASE, PubMed, OVID and Cochrane CENTRAL to identify included articles. The reference lists of relevant articles were searched, and in addition, studies were identified by authors with expertise in CIPN. Studies published from initial curation of the electronic database to March 2021 were identified, and those felt not relevant by authors were excluded with the guidance of the senior author (U.A.). This article is based on previously conducted studies and

does not contain any new studies with human participants or animals performed by any of the authors.

## TOXICITY VERSUS BENEFIT

Balancing the risk of different manifestations of chemotoxicity and the potential benefit of reduced disease burden/remission is a demanding aspect of oncological practice. For instance, there is an increased risk of CIPN with oxaliplatin compared to cisplatin, but the risk of thromboembolism is greater for cisplatin than for oxaliplatin [36], with a small survival benefit with oxaliplatin compared to cisplatin. Accordingly, there are many options to try to limit CIPN by reducing the number of doses and cumulative toxicity, especially in older individuals or those more likely to have pre-existing neuropathy such as diabetes [37]. Patients are less likely to continue chemotherapy if they develop serious complications. In a population of older patients in a non-curative setting, lower doses of oxaliplatin and capecitabine were better tolerated, resulting in patients receiving a greater number of cycles and a small survival benefit [37]. Al-Batran et al. [38] reported that the rate of CIPN in patients treated with epirubicin, cisplatin and fluoropyrimidine was half that observed in patients treated with oxaliplatin, docetaxel and fluoropyrimidine. Similarly, Cunningham et al. [36] reported that the rate of thromboembolism doubled in patients treated with epirubicin, cisplatin and fluoropyrimidine [38]. Ultimately, there are trade-offs when treating patients with cancer, especially those with limited therapeutic options, worse prognosis or pre-existing conditions that may predispose them to chemotherapy-related complications.

## OXALIPLATIN-INDUCED PERIPHERAL NEUROPATHY

Platinum-based chemotherapeutics (oxaliplatin, cisplatin and carboplatin) are used in the treatment of solid tumours of the gut, bladder, testes, ovary, uterus, lung, head and neck

**Table 1** The incidence of chemotherapy-induced peripheral neuropathy of participants undergoing platinum, taxane, vinca-alkaloid, immunomodulatory or proteasome inhibitor-based chemotherapy regimens

Study and design	Participants	Agent(s) studied	Cancer types	Diagnostic methodology	Grading criteria used	Study duration/length of follow-up	Incidence
<b>Platinum agents</b>							
Leonard et al. [298]; Phase I trial	Oxaliplatin ( <i>n</i> = 86)	Oxaliplatin	Colorectal	Questionnaire asked by clinical staff (SRO)	OSNS, based on the NCI-CTC	Up to 12 cycles	Grade 1 dysaesthesia: 70.9%, paraesthesia: 66.3%, grade 2 dysaesthesia: 11.6%, paraesthesia: 19.8%, grade 3 dysaesthesia: 4.7%, paraesthesia: 7%, grade 4 dysaesthesia: 0%, paraesthesia: 1.2%
Alejandro et al. [299]; Retrospective review of cohort study	FOLFOX6 ( <i>n</i> = 50)	FOLFOX6	Colorectal	NCI-CTC	NCI-CTC	Up to 12 cycles	84% reported at least one episode of acute neuropathy, 74% reported acute OIPN. 48% reported persistent OIPN. 12% reported grade 3 neuropathy > 8 cycles of FOLFOX
Rothenberg et al. [300]; Phase III trial	Total ( <i>n</i> = 445), Oxaliplatin ( <i>n</i> = 153), FOLFOX4 ( <i>n</i> = 150) fluorouracil and leucovorin ( <i>n</i> = 142)	Oxaliplatin, FOLFOX, fluorouracil and leucovorin	Metastatic colorectal	Questionnaire asked by clinical staff (SRO)	OSNS, based on the NCI-CTC	14 months (maximum)	Acute OIPN (all grades): 53–58%, acute OIPN grade 3–4: 3–10%, cumulative OIPN: 51%, cumulative OIPN grade 3–4: 3%
Yamada et al. [301]; Phase III trial	Total ( <i>n</i> = 685) S-1 and Oxaliplatin ( <i>n</i> = 318), S-1 and Cisplatin ( <i>n</i> = 324)	S-1 and oxaliplatin S-1 and cisplatin	Advanced gastric	SRO	NCI-CTC-AE	25.9 (median)	Oxaliplatin—sensory neuropathy (any grade): 85.5%, grade ≥ 3: 16%, cisplatin sensory neuropathy (any grade): 23.6%, grade ≥ 3: 0%
Bando et al. [302]; Phase III trial	Total ( <i>n</i> = 685) S-1 and oxaliplatin ( <i>n</i> = 343) S-1 and cisplatin ( <i>n</i> = 342)	S-1 and oxaliplatin S-1 and cisplatin	Advanced gastric	SRO	NCI-CTC-AE	17.5 months for oxaliplatin, 13.5 months for cisplatin (median)	OIPN grade ≥ 3 4.5–5.3%, CisPN grade ≥ 1: 0%
Lonardi et al. [303]; Phase III multicentre trial	Total ( <i>n</i> = 3715) 3 months FOLFOX/XELOX treatment ( <i>n</i> = 1848) 6 months FOLFOX/XELOX treatment ( <i>n</i> = 1867)	FOLFOX4 (64%) or XELOX (36%)	Stage II/III colorectal	NCI-CTC (SRO)	NCI-CTC	3 Years	3 months treatment with either FOLFOX or XELOX, grade 0: 49.9%, grade 1–2: 41.3%, grade 3–4: 8.8%, 6 months treatment with either FOLFOX or XELOX, grade 0: 31.6%, grade 1–2: 37.2%, grade 3–4: 31.2%
Al-Baraan et al. [304]; Phase III trial	Total ( <i>n</i> = 220) Oxaliplatin ( <i>n</i> = 112) Cisplatin ( <i>n</i> = 102)	Fluorouracil, leucovorin, and oxaliplatin Fluorouracil, leucovorin, and cisplatin	Advanced gastro-oesophageal	NCI-CTC (SRO)	WHO toxicity criteria	14 months (median)	Oxaliplatin (all grades): 62.5%, oxaliplatin grade 3–4: 14.3%, cisplatin (all grades): 21.6%, cisplatin grade 3–4: 2%
Cassidy et al. [305]; Two-arm, open-label, randomised phase III trial	Total ( <i>n</i> = 1304) FOLFOX4 ± placebo ( <i>n</i> = 649) XELOX ± placebo ( <i>n</i> = 655)	FOLFOX4, XELOX	Colorectal	NCI-CTC (SRO)	NCI-CTC	29.7 months (median)	FOLFOX4, grade 1: 11%, grade 2: 5%, grade 3: 4%, grade 4: 0%, XELOX, grade 1: 11%, grade 2: 5%, grade 3: 4%, grade 4: 0%
Tournigand et al. [306]; Randomised FOLFOX comparator trial	Total ( <i>n</i> = 620) FOLFOX4 ( <i>n</i> = 311) FOLFOX7 + simplified leucovorin and fluorouracil ( <i>n</i> = 309)	FOLFOX4, FOLFOX7, leucovorin, fluorouracil	Advanced colorectal	NCI-CTC (SRO)	NCI-CTC	31 months (median)	FOLFOX4, grade 1: 34%, grade 2: 37%, grade 3: 18%, grade 4: 0%, FOLFOX7, grade 1: 36%, grade 2: 42%, grade 3: 13%, grade 4: 0%

**Table 1** continued

Study and design	Participants	Agent(s) studied	Cancer types	Diagnostic methodology	Grading criteria used	Study duration/length of follow-up	Incidence
Andre et al. [307]: International phase III trial	Total ( <i>n</i> = 2246) Oxaliplatin + fluorouracil and leucovorin ( <i>n</i> = 1123) Fluorouracil and leucovorin ( <i>n</i> = 1123)	Oxaliplatin, fluorouracil, leucovorin	Stage II/III colorectal	NCI-CTC (SRO)	NCI-CTC (version 1.0)	-	Oxaliplatin + fluorouracil and leucovorin, paraesthesia, all grades: 92%, grade 3: 12.4%, fluorouracil and leucovorin, all grades: 15.6%, grade 3: 0.2%
Gebremedhn et al. [42]: Systematic review	Total participants treated with oxaliplatin ( <i>n</i> = 6211)	FOLFOX, FOLFOX3, FOLFOX4, oxaliplatin, XELOX	-	NCI-CTC version 1, 2 and 3, TNSc, WHO toxicity criteria, FACT, OSNS	-	-	Acute OIPN: most common AE of all grades 4–98%
Bejers et al. [308]: Systematic review	Total participants treated with oxaliplatin ( <i>n</i> = 3869)	FOLFOX, FOLFOX4, XELOX	-	NCI-CTC version 1, 2 and 3, TNSc, WHO toxicity criteria, FACT, OSNS, NCS	-	12 months–8 years	No definitive conclusions drawn for the incidence and risk factors for chronic OIPN
Land et al. [309]: Phase III trial	Total ( <i>n</i> = 395) Oxaliplatin, fluorouracil and leucovorin ( <i>n</i> = 189) Fluorouracil and leucovorin ( <i>n</i> = 206)	Oxaliplatin, fluorouracil and leucovorin	Stage II/III colorectal	FACT, OSNS, NCI-CTC	-	18 months	OIPN at 12 months, grade 1: 25%, grade 2: 4.5%, grade 3: 0.4%
De Gramont et al. [46]: Phase III trial	Total ( <i>n</i> = 420) Oxaliplatin, fluorouracil and leucovorin ( <i>n</i> = 210) Fluorouracil and leucovorin ( <i>n</i> = 210)	Oxaliplatin, fluorouracil and leucovorin	Colorectal	NCI-CTC	NCI-CTC	27.7 months (median)	Painless paraesthesia: 65.1%, painful paraesthesia: 10.5%, pharyngolaryngeal dysaesthesia: 22.5%
Briani et al. [47]: Longitudinal cohort study	Total ( <i>n</i> = 91)	FOLFOX4, FOLFOX6, XELOX	Colorectal	NCI-CTC, neurological examination, TNSc and NCS	TNSc	25 months (median) after treatment cessation	After 2 years treatment cessation: OIPN, grade 1: 85.2%, grade 2: 14.8%, grade 3: 0%
Park et al. [43]: Longitudinal cohort study	Total ( <i>n</i> = 24)	FOLFOX4, FOLFOX6, XELOX	Colorectal	Clinical examination, TNSc, NSS, NCI-CTC (Sensory subscale), NCS	TNSc, NCI-CTC (Sensory subscale)	29 ± 4 months after treatment cessation	After 2.4 years treatment cessation: persistent OIPN symptoms: 79.2% (upper limbs 45.8%, 79.2% in the lower limbs), grade 0: 20.8%, grade 1: 37.5%, grade 2: 29.2%, grade 3: 12.5%, 66.7% reported minor improvements of 1 grade during time to follow-up > 40% reported fine motor deficits, walking difficulties and significant functional impairments

**Table 1** continued

Study and design	Participants	Agent(s) studied	Cancer types	Diagnostic methodology	Grading criteria used	Study duration/length of follow-up	Incidence
Ibrahim et al. [310]: multicentre randomised trial enrolled	Total ( <i>n</i> = 445) Oxaliplatin, fluorouracil and leucovorin ( <i>n</i> = 150) Fluorouracil and leucovorin ( <i>n</i> = 142) Oxaliplatin ( <i>n</i> = 153)	Oxaliplatin, fluorouracil and leucovorin	-	WHO toxicity criteria, NCI-CTC	NCI-CTC	-	Oxaliplatin (all grades), total: 76%, acute: 65%, chronic: 43%, oxaliplatin (grade 3/4), acute: 5%, chronic: 3%, oxaliplatin, fluorouracil and leucovorin (all grades), total: 74%, acute: 56%, chronic: 48%, oxaliplatin, fluorouracil and leucovorin (grade 3/4), acute: 2%, chronic: 6%
<b>Taxanes</b>							
Argyriou et al. [311]: Prospective study	Total ( <i>n</i> = 21)	Paclitaxel, carboplatin	Lung, breast, ovarian	NSS, NDS, NCS	PNP, WHO toxicity criteria	3 months	Neuropathy (all grades): 66.5%, none: 33.3%, mild: 19%, moderate: 33.3%, severe: 14.2%
Peng et al. [312]: Meta-analysis	Total ( <i>n</i> = 2878)	Nab-paclitaxel	Gastric, urothelial, pancreatic, lung breast, cervix, ovarian, melanoma and prostate	-	NCI-CTC (version 4.0)	-	Nab-paclitaxel TIPN, total (all grades): 51.0% (95% CI 45.1–57.6%), high-grade: 12.4% (9.8–15.7%)
Socinski et al. [313]: Phase III trial	Total ( <i>n</i> = 1052) Nab-paclitaxel + carboplatin ( <i>n</i> = 521) Paclitaxel + carboplatin ( <i>n</i> = 531)	Nab-paclitaxel, paclitaxel, carboplatin	Advanced non-small cell lung	ECOG, NCI-CTC (version 3.0)	NCI-CTC (version 3.0)	-	Nab-paclitaxel group, TIPN (all grades): 46%, grade 3: 3%, grade 4: 0%, paclitaxel group TIPN (all grades): 62%, grade 3: 11%, grade 4: < 1%
Pace et al. [241]: Pilot study	Total ( <i>n</i> = 14)	Paclitaxel	Advanced breast	Neurological examination (VPT, pinprick, muscle strength, deep tendon reflexes), TNS, NCS	-	24 weeks, for 11 participants, a further follow-up examination was conducted 4–17 months after cessation of treatment	TIPN (all grades), 12 weeks: 71% (paraesthesia ± impaired tendon reflexes), 14 weeks: 96% (signs ± symptoms ± significant NCS abnormalities), non-significant improvement in all patients at follow-up
Baldwin et al. [314]: Prospective cohort study	Total ( <i>n</i> = 1940)	Paclitaxel	Breast	NCI-CTC (version 2.0)	NCI-CTC (version 2.0)	-	TIPN grade ≥ 2, 4 cycles of paclitaxel: 17%, 6 cycles of paclitaxel: 33%
Dorling et al. [315]: Secondary case-control study of four chemotherapy trials	Total ( <i>n</i> = 2354) Participants analysed according to NCI-CTC-AE ( <i>n</i> = 1279)	Paclitaxel, gemcitabine, cyclophosphamide, methotrexate, 5-fluorouracil, epirubicin	Breast	NCI-CTC-AE (version 2.0 & 3.0), TNS	NCI-CTC-AE (version 2.0 & 3.0)	1 month after treatment cessation	TIPN, grade 0: 21.2%, grade 1: 50.7%, grade 2: 23.7%, grade 3: 4.4%, TIPN grade ≥ 2: 28.1%



**Table 1** continued

Study and design	Participants	Agent(s) studied	Cancer types	Diagnostic methodology	Grading criteria used	Study duration/length of follow-up	Incidence
Shimozuma et al. [84]: Phase III trial	Total ( <i>n</i> = 300)						Anthracycline + cyclophosphamide + paclitaxel ( <i>n</i> = 74) Anthracycline + cyclophosphamide + docetaxel ( <i>n</i> = 75), Paclitaxel ( <i>n</i> = 76) Docetaxel ( <i>n</i> = 75)
Anthracycline,	cyclophosphamide paclitaxel, docetaxel	Breast	PNQ, FACT, NCI-CTC (version 2.0)	PNQ	1 year	Incidence of PNQ grade D or E (equivalent to NCI-CTC grade 3–4) for: paclitaxel: > 10%, docetaxel: > 10%, both worsened after cycles 3–7, with an incidence of 16–21%	
Scagliotti et al. [316]: Phase III trial	Total ( <i>n</i> = 926)						Paclitaxel + carboplatin + sorafenib ( <i>n</i> = 464) Paclitaxel + carboplatin + placebo ( <i>n</i> = 462)
Paclitaxel, carboplatin, sorafenib	Advanced non-small cell lung	NCI-CTC-AE (version 3.0)	NCI-CTC-AE (version 3.0)	~ 10 months	Paclitaxel, carboplatin, sorafenib group, all grades: 14%, grade 3: 3%, paclitaxel, carboplatin, placebo group, all grades: 13%, grade 3: 2%		
Bonomi et al. [83]: Phase III trial	Total ( <i>n</i> = 574) High-dose paclitaxel and cisplatin ( <i>n</i> = 193) Low-dose paclitaxel and cisplatin ( <i>n</i> = 191) Etoposide and cisplatin ( <i>n</i> = 190)	Paclitaxel, etoposide, cisplatin,	Advanced non-small cell lung	ECOG, FACT	ECOG	28.5 months (median)	Grade 3 TIPN, high-dose paclitaxel and cisplatin: 40%, low-dose paclitaxel and cisplatin: 25%, etoposide and cisplatin: 21%
Scagliotti et al. [317]: Phase III trial	Total ( <i>n</i> = 607) Paclitaxel + carboplatin ( <i>n</i> = 201) Gemcitabine + cisplatin ( <i>n</i> = 205) Vinorelbine + cisplatin ( <i>n</i> = 201)	Paclitaxel, carboplatin, gemcitabine, cisplatin, vinorelbine	Advanced non-small cell lung	NCI-CTC (version 2.0)	NCI-CTC (version 2.0)	8–10 months	CIPN in paclitaxel and carboplatin group, grade 1: 22.8%, grade 2: 7%, grade 3: 0%, CIPN in the cisplatin and gemcitabine, grade 1: 4%, grade 2: 0%, grade 3: 0%, CIPN in the vinorelbine and cisplatin, grade 1: 4%, grade 2: 2.5%, grade 3: 0.5%



**Table 1** continued

Study and design	Participants	Agent(s) studied	Cancer types	Diagnostic methodology	Grading criteria used	Study duration/length of follow-up	Incidence
Gao et al. [318]: Meta-analysis	Total ( <i>n</i> = 940)	Paclitaxel	Advanced, non-small cell lung	-	-	-	Weekly paclitaxel treatment grade 3–4: 10%, once every 3 weeks paclitaxel treatment, grade 3–4: 17.92%
<b>Vinca alkaloids</b>							
Ness et al. [107]: Cohort study (children)	Total ( <i>n</i> = 531)	Vincristine, vinblastine, carboplatin, cisplatin	Skin, brain, bone, muscle and kidney	mTNS, SOT	mTNS	Participants underwent testing ≥ 10 years after treatment	Sensory neuropathy (all grades): 20.4%, motor neuropathy (all grades): 20.8%
Andersson et al. [108]: Cohort study	Total ( <i>n</i> = 107)	Vinorelbine	Advanced or metastatic breast	MedRA (version 18.1)	MedRA (version 18.1)	26.5 months (median)	Any grade: 21.5%, grade 3–4: 1.9%
Ramchandren et al. [319]: Cohort study (children)	Total ( <i>n</i> = 37)	Vincristine	Acute lymphoblastic leukaemia	NIS, NCS, TNSr	NIS, NCS, TNSr	Participants underwent testing 7.4 years after treatment (mean)	TNSr: score of 1 indicated a VIPN prevalence of 100%, TNSr score of ≥ 2 indicated a VIPN prevalence of 94.6%. Participants had impaired NCS
Smith et al. [320]: Cohort study (children)	Total ( <i>n</i> = 128)	Vincristine	Acute lymphoblastic leukaemia	NCI-CTC-AE (version 4.0)	NCI-CTC-AE (version 4.0)	1 year from start of treatment	VIPN (all grades): 78%, sensory VIPN: grade 1: 31%, grade 2: 3.2%, grade 3: 1.6%, grade 4: 0%, motor VIPN: grade 1: 18%, grade 2: 4.4%, grade 3: 1.9%, grade 4: 0%
<b>Immunomodulatory agents</b>							
Glasmacher et al. [133]: Systematic review and pooled analysis	Total ( <i>n</i> = 1674)	Thalidomide	Multiple myeloma	WHO toxicity criteria	WHO toxicity criteria	-	50–200 mg/day of bortezomib: 16% BIPN (all grades), ≥ 200 mg/d of bortezomib: 31% BIPN (all grades)
Mileskhin et al. [125]: Cohort study	Total ( <i>n</i> = 75)	Thalidomide	Refractory/relapsed multiple myeloma	NCI-CTC (version 2.0), NCS	NCI-CTC (version 2.0)	24 weeks	Grade ≥ 2 ThIPN: 31% SNAP impairment (> 50%): 53%
Dimopoulos et al. [321]: Multicentre phase II Trial	Total ( <i>n</i> = 44)	Thalidomide, dexamethasone	Refractory multiple myeloma	WHO toxicity criteria	WHO toxicity criteria	23.3 months (median)	ThIPN (all grades): 23%
Prince et al. [322]: Multicentre phase II Trial	Total ( <i>n</i> = 66)	Thalidomide	Relapsed/resistant multiple myeloma	NCI-CTC (version 2.0), NCS	NCI-CTC (version 2.0), NCS	20 months (median)	ThIPN (all grades): sensory: 70%, motor: 35%, ThIPN grade 3: sensory: 11%, motor: 3%
von Lilienfeld-Toal et al. [323]: Systematic review and pooled analysis	Total ( <i>n</i> = 451)	Thalidomide, dexamethasone	Refractory/relapsed multiple myeloma	-	-	-	ThIPN (all grades): 27% (95% CI 23–32)

**Table 1** continued

Study and design	Participants	Agent(s) studied	Cancer types	Diagnostic methodology	Grading criteria used	Study duration/length of follow-up	Incidence
Briani et al. [121]: Case-control study	Total ( <i>n</i> = 14)	Thalidomide	Systemic lupus erythematosus	Neurological examination, NSS, NCS	Neurological examination, NSS, NCS	Up to 35 months	ThIPN (all grades): 71.4%
Grover et al. [325]: Case-control study	Total ( <i>n</i> = 23)	Thalidomide, cyclophosphamide, vincristine	Refractory/relapsed multiple myeloma	-	-	Up to 15 months	ThIPN (all grades): 13%
Tosi et al. [130]: Longitudinal Cohort study	Total ( <i>n</i> = 40)	Thalidomide	Refractory/relapsed multiple myeloma	WHO toxicity criteria	WHO Toxicity Criteria	1 year	ThIPN at 6 months, grade 0: 47.5%, grade 1: 35%, grade 2: 17.5%, grade 3: 0%, ThIPN at 1 year, grade 0: 25%, grade 1: 15%, grade 2: 32.5%, grade 3: 27.5%
Facon et al. [326]: Randomised controlled trial	Total ( <i>n</i> = 447) Melphalan + prednisone ( <i>n</i> = 196)	-	-	30 months	ThIPN (all grades): 55%, grade 3 – 5%	-	Melphalan + prednisone + thalidomide ( <i>n</i> = 125) Stem cell transplant + melphalan ( <i>n</i> = 126)
Thalidomide, melphalan, prednisone	Multiple myeloma	-	-	30 months	ThIPN (all grades): 55%, grade 3 – 5%	-	-
Bastuji-Garin et al. [122]: Prospective Cohort Study	Total ( <i>n</i> = 135)	Thalidomide	Dermatological disorder	Signs and symptoms, NCS	Signs and symptoms, NCS	30 months	ThIPN (all grades): 25.2% (95% CI 17.9–32.5%)
Bramuzzo et al. [120]: Multicentre cohort study (children)	Total ( <i>n</i> = 142)	Thalidomide	Pediatric inflammatory bowel disease	NCI-CTC (version 4.0), NCS	NCI-CTC (version 4.0)	24 months	ThIPN (all grades): 72.5%, NCS impairment 49.1%
Dimopoulos et al. [135]: Phase III trial	Total ( <i>n</i> = 351) Lenalidomide ( <i>n</i> = 176) Placebo ( <i>n</i> = 175)	Lenalidomide	Refractory/relapsed multiple myeloma	NCI-CTC (version 2.0)	NCI-CTC (version 2.0)	11.3 months (median)	Grade 3 lenalidomide-related neuropathy occurred at < 10%
Briani et al. [136]: Prospective Cohort Study	Total ( <i>n</i> = 30)	Lenalidomide	Refractory/relapsed multiple myeloma	TNS, ECOG	TNS, ECOG	12 months	At baseline 53.3% of patients had BIPN/ThIPN; these patients remained stable. No lenalidomide-related neuropathy was identified after 12 months

**Table 1** continued

Study and design	Participants	Agent(s) studied	Cancer types	Diagnostic methodology	Grading criteria used	Study duration/length of follow-up	Incidence
Miguel et al. [137]: Multicentre phase III trial	Total ( <i>n</i> = 455), Pomalidomide + low-dose dexamethasone ( <i>n</i> = 302), high-dose dexamethasone ( <i>n</i> = 153)	Pomalidomide, dexamethasone	Refractory/relapsed multiple			myeloma + intolerant to bortezomib, lenalidomide or thalidomide	ECOG
ECOG	18 months	Pomalidomide-related neuropathy (any grade): 15%, dexamethasone-related neuropathy (any grade): 11%, pomalidomide or dexamethasone-related neuropathy (grade ≥ 3): 1%					
Richardson et al. [327]: Multicentre phase II trial	Total ( <i>n</i> = 102) 15 mg of lenalidomide twice daily ( <i>n</i> = 35) 30 mg of lenalidomide once daily ( <i>n</i> = 67)	Lenalidomide	Refractory/relapsed multiple myeloma	NCI-CTC (version 2.0)	NCI-CTC (version 2.0)	28 months	Lenalidomide-related neuropathy observed in 10% of patients in the once-daily group, lenalidomide-related neuropathy observed in 2.3% of patients in the twice-daily group
Katodritou et al. [132]: Cohort study	Total ( <i>n</i> = 211)	Lenalidomide, dexamethasone	Refractory/relapsed multiple myeloma	-	-	13 months (median)	Lenalidomide-related neuropathy observed in 8% of patients
Proteasome inhibitors							
Peng et al. [328]: Meta-analysis	Total ( <i>n</i> = 6492)	Bortezomib	Multiple myeloma, mantle cell lymphoma	-	-	-	BIPN (all grades): 33.9% (95% CI 29.9–38.5%), BIPN grade 3/4: 8.1% (95% CI 6.9–9.4%)
Richardson et al. [153]: Phase II trial	Total ( <i>n</i> = 193)	Bortezomib	Multiple myeloma	NCI-CTC (version 2.0)	NCI-CTC (version 2.0)		BIPN (all grades): 31%, BIPN grade 3: 12%
Richardson et al. [129]: Cohort study	Total ( <i>n</i> = 256) Bortezomib at 1 mg/m <sup>2</sup> ( <i>n</i> = 28) Bortezomib at (1.3 mg/m <sup>2</sup> ) ( <i>n</i> = 228)	Bortezomib	Advanced multiple myeloma	FACT, GOG-Ntx	FACT, GOG-Ntx	-	BIPN (1 mg/m <sup>2</sup> ), grade 1: 11% grade 2: 4%, grade 3: 4% grade 4: 4%, all grades: 21%, BIPN (1.3 mg/m <sup>2</sup> ), grade 1: 7%, grade 2: 16%, grade 3: 14%, grade 4: 0%, All grades: 37%
Richardson et al. [329]: Phase III trial	Total ( <i>n</i> = 669) Bortezomib ( <i>n</i> = 331) dexamethasone ( <i>n</i> = 332)	Bortezomib, dexamethasone	Advanced multiple myeloma	NCI-CTC (version 2.0)	NCI-CTC (version 2.0)	-	BIPN (all grades): 36%, BIPN grade 3): 7%, BIPN grade 4): 1%
Richardson et al. [330]: Cohort study	Total ( <i>n</i> = 64)	Bortezomib	Multiple myeloma	FACT, GOG-Ntx, NCS	NCI-CTCAE (version NS)	29 months (median)	BIPN (all grades): 64%, grade 1: 36%, grade 2: 25%, grade 3: 3%

**Table 1** continued

Study and design	Participants	Agent(s) studied	Cancer types	Diagnostic methodology	Grading criteria used	Study duration/length of follow-up	Incidence
Kropff et al. [154]: Phase II trial	Total (n = 54)	Bortezomib, dexamethasone, cyclophosphamide	Multiple myeloma	NCI-CTC (version 3.0)	NCI-CTC (version 3.0)	20 months (median)	BIPN, grade 1: 17%, grade 2: 28%, grade 3: 17%
Aguiar et al. [331]: Systematic review and meta-analysis	-	Bortezomib, thalidomide, lenalidomide	Multiple myeloma	-	-	-	Peripheral neuropathy incidence was significantly higher when thalidomide was added to chemotherapy regimens compared to control arms
Chaudhry et al. [127]: Prospective cohort study	Total (n = 27)	Bortezomib, thalidomide	Multiple myeloma	TNS, NCS	TNS	2 months (median)	All grades: 96%, grade 1: 42%, grade 2: 38%, grade 3: 19%

*CIPN* chemotherapy-induced peripheral neuropathy, *CisPN* cisplatin-induced peripheral neuropathy, *ECOG* Eastern Cooperative oncology group criteria, *FACT* Functional Assessment of Cancer Therapy, *GOG-Nx* Gynecologic Oncology Group–Neurotoxicity, *NCS* nerve conduction studies, *NDS* Neuropathy Disability Score, *NIS* Neuropathy Impairment Score, *NS* not stated, *NSS* Neuropathy Symptom Score, *MeDRA* Medical Dictionary for Regulatory Activities, *OSNS* oxaliplatin-specific neurotoxicity scale, *PNP* modified peripheral neuropathy score, *PNQ* Patient Neurotoxicity Questionnaire, *OIPN* oxaliplatin-induced peripheral neuropathy, *SOT* sensory organisation test, *SRO* self-reported outcome, *TbIPN* thalidomide-induced peripheral neuropathy, *TIPN* taxane-induced peripheral neuropathy, *TNS* Total Neuropathy Score, *TNSy* Total Neuropathy Score–reduced, *mTNS* modified Total Neuropathy Score, *VPT* vibration perception threshold

[39, 40]. Platinum chemotherapeutic agents have the highest prevalence rates of CIPN, affecting ~ 70% of patients, often complicated by coasting [29, 41]. The main anatomical structure injured by platinum agents is the dorsal root ganglion, and manifests as a sensory neuropathy with prominent pain accompanied by cold-induced allodynia and muscle cramps due to peripheral nerve hyperexcitability or neuromyotonia. Acute oxaliplatin-induced peripheral neuropathy (OIPN) can result in prolonged infusion times (~ 22%), dose reduction (15–43%) and treatment cessation (6–21.4%) [42–46]. A systematic analysis of studies including 6211 participants undergoing oxaliplatin treatment found acute OIPN with an incidence of 4–98% [42]. The wide range of incidence may be attributed to heterogeneous dosing regimens, drug combinations, dosing intervals and screening instruments used to identify acute OIPN [42]. A longitudinal study following 346 participants undergoing FOLFOX chemotherapy demonstrated a 3-day peak in acute OIPN, with sensory symptoms including cold-induced hypersensitivity (71%), sensitivity to swallowing cold food and drink (71%), throat discomfort (63%) and muscle cramps (42%) [25]. Symptoms often persist between treatments and increase in severity with subsequent doses [25, 26]. The initial severity of acute OIPN also predicts progression to chronic sensory OIPN [25, 47], which can be identified in 84% of patients after 25 months, with long-term impact on functionality and quality of life.

## PATHOGENESIS OF PLATINUM-INDUCED PERIPHERAL NEUROPATHY

The dorsal root ganglion (DRG) is particularly susceptible to chemotherapeutic agents, as it lies outside the central nervous system and is not protected by the blood–brain barrier [48]. In an animal model of CIPN, the accumulation of oxaliplatin in DRG neurons was associated with intracellular overexpression of Octn1/2 and Mate1 transporters [49]. Oxaliplatin also interferes with DNA cross-linking, resulting in direct neurotoxicity [50] and early p38 and ERK1/2

activation, reduced mitochondrial respiration, increased oxidative stress and dose-dependent apoptosis of DRG neurons [51]. Cell culture studies have shown greater neuronal cell body atrophy and apoptosis when exposed to oxaliplatin compared to both paclitaxel and controls, promoting a sensory neuropathy (neuronal cell body) as opposed to an axonopathy that is phenotypic of other chemotherapeutic agents. OIPN also correlates with mitochondrial morphological artefacts, decreased adenosine triphosphate generation and depressed respiration rates in mitochondrial complexes I and II [52–54] 55. Indeed, platinum agents and their metabolites form adducts with mitochondrial DNA (mtDNA), disrupting replication and transcription, with a reduction in neuronal cell body mitochondrial populations [56]. Oxidative stress leads to oxidation of intracellular moieties of neurons, diminishing neuronal energy status and increasing apoptosis [55, 57–61]. Reduction of oxidative stress with phenyl *N*-tert-butyl nitron has been shown to decrease oxaliplatin-induced mechanical hyperalgesia and cold allodynia [62, 63]. Oxaliplatin also interacts with voltage-gated potassium channels (VGKC) expressed on peripheral motor neurons and is implicated in the acute phase of OIPN in which patients exhibit nerve hyperexcitability, prolonged depolarisation, increased neurotransmission and muscle contraction similar to that seen in neuromyotonia [44]. Notably, the excitability of A $\delta$  and C-type fibres of the maxillary branch of the trigeminal nerve are controlled by VGKCs. Further, VGKC isotype 4.3 channels had slower deactivation after administration of oxaliplatin, and this may underlie cold-induced orofacial allodynia [64]. Intramuscular injections at the base of the tail of mice with oxaliplatin were shown to cause acute transient dose-dependent changes in excitability of both motor and sensory axons and evoked ectopic activity in these fibres [65]. Moreover, mathematical modelling indicates that oxaliplatin causes slow inactivation of voltage-gated sodium (NaV) channels and reduces the resting membrane potential of nerve fibres through the reduction of fast potassium conductance in the acute phase of OIPN [65]. Indeed, in preclinical studies, NaV

**Table 2** Neurotoxic antineoplastic agents and their cumulative dose, symptoms and signs [9, 10, 14, 23–28, 42, 43, 46, 47, 102, 107, 108, 120–123, 127, 129, 134, 184, 187, 241, 260, 298, 307, 320, 321, 323–325, 329, 334–352]

Antineoplastic agent	Approval	Cumulative toxic dose	Symptoms/Signs	Progression
Oxaliplatin (acute)	2002 <sup>a</sup>	≥ 85 mg/m <sup>2</sup>	Predominantly sensory acute: Cold-induced allodynia, throat discomfort, tingling, numbness ± pain in the hands and feet	Acute (may lead to dose reduction or stopping treatment)
				Does not resolve between cycles
			Predominantly sensory chronic: Distal and symmetrical loss of sensation in the hands and feet ± pain	Severity of acute OIPN is predictive of chronic and higher grade
Oxaliplatin (chronic)		≥ 510 mg/m <sup>2</sup>	Symptoms are predominantly in the hands, which become more predominant in the feet after ~ 18 months of chronic OIPN symptoms	Coasting phenomenon Participants continue to report symptoms for years after treatment has stopped
Cisplatin	1985 <sup>a</sup>	≥ 600 mg/m <sup>2</sup>	Cisplatin implicated in ototoxicity  Motor: Muscle cramps, neuromyotonia, muscle weakness, fine motor impairment Reduction and/or loss of deep tendon reflexes Autonomic: Orthostatic hypotension	A proportion of participants recover although not back to pre-chemotherapy baseline
Carboplatin	1986 <sup>a</sup>	≥ 780 mg/m <sup>2</sup> ≥ 400 mg/m <sup>2</sup>	Sensory: Distal and symmetrical loss of sensation in the hands and feet: Motor: Large fibre involvement leading to ataxia Reduction or loss of deep tendon reflexes	Acute (may lead to dose reduction or stopping treatment) Can progress to chronic Coasting effect

Table 2 continued

Antineoplastic agent	Approval	Cumulative toxic dose	Symptoms/Signs	Progression
Taxanes			Paclitaxel acute pain syndrome: Aching pain, arthralgia, myalgia and muscle cramps in the lower extremities	Acute pain syndrome Acute symptoms may not resolve between cycles
Paclitaxel	1992 <sup>a</sup>	≥ 100 mg/m <sup>2</sup>	Predominantly sensory:	Severity of acute TIPN may lead to dose reduction or stopping treatment and is predictive of chronic and higher-grade neuropathy
Docetaxel	1995 <sup>a</sup>	≥ 300 mg/m <sup>2</sup>	Acute, length-dependent distal sensory neuropathy characterised by numbness and tingling ± pain in a stocking-and-glove distribution Neuropathic pain in the hands and feet is frequent	Recovery or improvement once treatment is stopped is expected in a majority of patients Participants recover although rarely back to pre-chemotherapy baseline
			Motor:	A number continue to persist with low-grade symptoms
			Reduction and/or loss of deep tendon reflexes Possible proprioceptive loss leading to an unsteady gait Facial nerve palsy Rare autonomic: Orthostatic hypotension Paralytic ileus Arrhythmia Optic neuropathy	
Vinca alkaloids			Predominantly sensorimotor: Distal and symmetrical loss of sensation in the hands and feet characterised by numbness and tingling ± pain	Acute (may lead to dose reduction or stopping treatment) Progression to chronic has established genetic risk factors



Table 2 continued

Antineoplastic agent	Approval	Cumulative toxic dose	Symptoms/Signs	Progression
Vincristine	1984 <sup>a</sup>	$\geq 4 \text{ mg/m}^2$	Motor:	Children and adolescents tolerate higher cumulative doses than adults
			Distal symmetric weakness in lower legs	
Vinblastine	1992 <sup>a</sup>		Walking difficulties	Coasting effect
			Muscle cramps	
Vinorelbine	1994 <sup>a</sup>		Foot drop	
			Impaired fine motor skills	
			Autonomic:	
			Orthostatic hypotension	
			Paralytic ileus	
			Constipation	
			Urogenital dysfunction	
			Walking difficulties	
			Foot drop	
			Impaired fine motor skills	

Table 2 continued

Antineoplastic agent	Approval	Cumulative toxic dose	Symptoms/Signs	Progression
Thalidomide	2003 <sup>a</sup>	≥ 50 mg/day	Sensory Distal and symmetrical loss of sensation in the hands and feet characterised by hyperaesthesia, hypoaesthesia and paraesthesia Numbness, tingling, burning pain, sensitivity to touch and heat in the hands and feet Motor Distal weakness, tremor Muscle cramps Reduction or loss of deep tendon reflexes Loss of proprioception Gait ataxia	Acute can progress to chronic Long-term neurotoxic sequelae are not uncommon Treatment duration may be more neurotoxic than dose
Bortezomib	2008 <sup>a</sup>	≥ 1 mg/m <sup>2</sup>	Sensory: Distal symmetrical, length-dependent axonal sensorimotor neuropathy, mild to moderate sensory loss, mild to severe neuropathic pain in a glove-and-stocking distribution. Burning sensations, tingling, hyperaesthesia, hypoaesthesia and weakness in the distal extremities, which may advance proximally Motor: Mild to moderate motor weakness in the distal lower extremities Rare autonomic: Orthostatic hypotension	Acute can progress to chronic, although a majority of participants improve or completely resolve BIPN

*OIPN* oxaliplatin-induced peripheral neuropathy, *TIPN* taxane-induced peripheral neuropathy

<sup>a</sup> Approval dates by a major governing body were compiled using Wishart et al. [353] DrugBank 5.0

channel-blocking drugs such as topiramate have recently been shown to have a neuroprotective effect in the prevention of both the acute and chronic phase of OIPN, with no interactions with the antineoplastic activity of oxaliplatin [66].

Cold hyperalgesia is a major feature of OIPN and is thought to be driven by TRPA1 and p38 MAPK activation in DRG neurons and increased activity of NaV channel isoforms NaV1.6 and NaV1.9 in nociceptive subpopulations of peripheral and DRG neurons. Further, there is a potential role played by transient receptor potential melastatin 8 (TRPM8) in acute cold-induced allodynia [67]. Altered expression of pain receptor-associated TREK-1, TRAAK, TRPA1 NaV channel isoforms and hyperpolarisation-activated cyclic nucleotide-gated (HCN1) channels in sensory neurons contribute to the prominent neuropathic pain associated with this condition [68]. Oxalate chelates  $\text{Ca}^{2+}$  ions, contributing to neuronal excitability and increasing spontaneous pain signalling [69]. There is also increased expression of pro-inflammatory cytokines including tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin (IL)-1 $\beta$  and decreased expression of the neuroprotective cytokines IL-10 and IL-4 [70–72] through the activation of astrocytes by platinum-based chemotherapy agents. A summary figure of these processes is shown in Fig. 1.

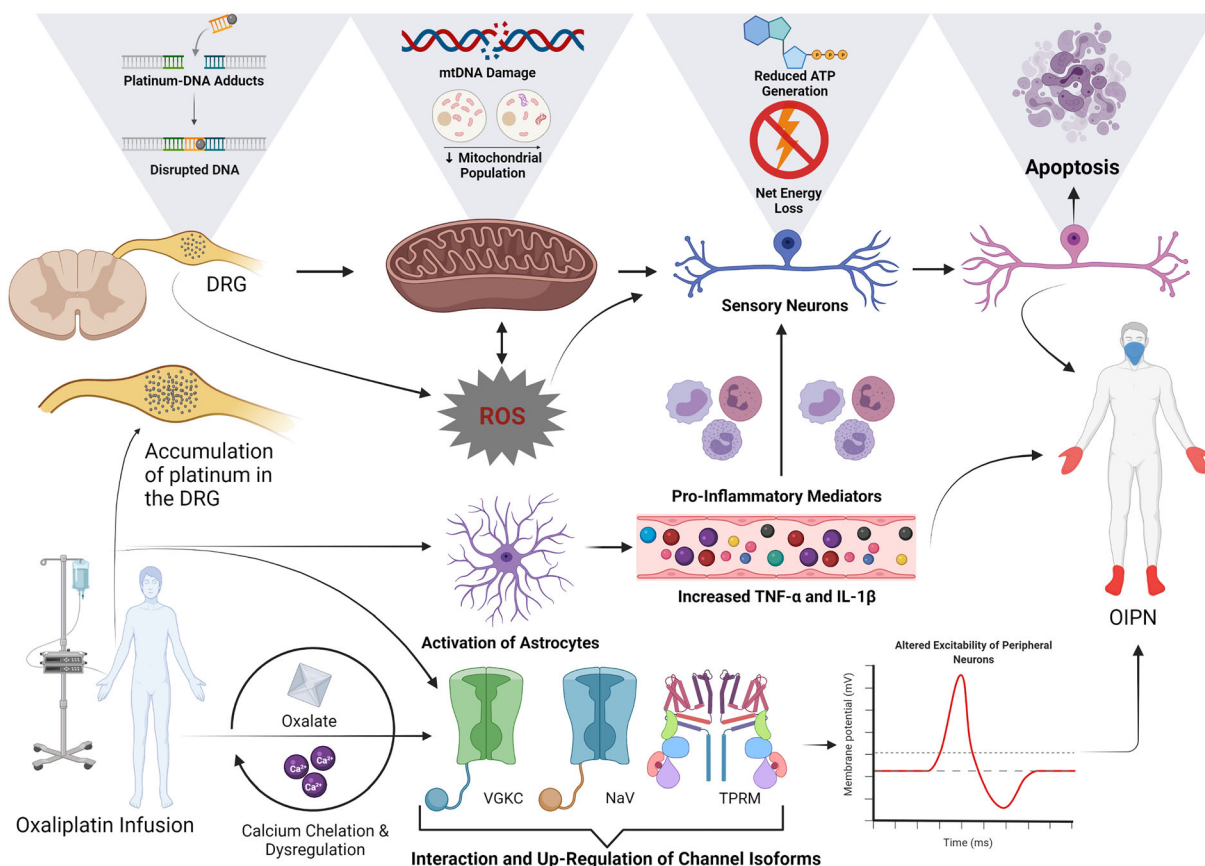
## TAXANE-INDUCED PERIPHERAL NEUROPATHY

The taxanes (paclitaxel, docetaxel and cabazitaxel) are currently first-line treatments for breast, ovarian, lung, bladder, prostate and other solid tumour cancers [34, 73, 74]. Taxane-induced peripheral neuropathy (TIPN) is the most common non-haematological adverse event of treatment, which may result in dose reduction and cessation of treatment, impacting patient survival [75]. TIPN primarily causes an acute, length-dependent distal sensory neuropathy, accompanied by neuropathic pain, which may progress proximally in more severe cases. A $\beta$  fibres and to a lesser extent A $\delta$  and C-fibres are affected in a glove-and-stocking

distribution [31, 76, 77]. Patients report tingling, numbness, paraesthesia, neuropathic pain, cold-induced dysaesthesia and muscle cramps [26, 78], which typically worsen with treatment and gradually improve with cessation [26], although 31–44% of patients treated with docetaxel or paclitaxel report symptoms after up to 6 years of follow-up [79–81]. TIPN incidence in non-small cell lung cancer (NSCLC) in phase III trials occurred in 13–62% of patients [82]. Severe TIPN (FACT-Lung grade  $\geq 3$ ) occurred in 21–40% of patients, with worse outcomes after receiving paclitaxel as opposed to docetaxel-based chemotherapy regimens [83]. Thus, docetaxel is generally considered to be less neurotoxic than paclitaxel [84].

## PATHOGENESIS OF TIPN

Studies have identified an increase in the incidence of abnormal axonal mitochondria in C-fibres when compared to controls after  $\sim 1$  month of paclitaxel treatment [85]. Paclitaxel interacts with the mitochondrial permeability transition pore, leading to mitochondrial dysfunction, decreased mitochondrial respiration and disruption of neuronal ATP generation [86, 87], with disruption of the axonal microtubule network [88]. Taxane treatment of rat DRG neuronal stem cells increased ROS production and oxidative stress, simultaneously decreasing mitochondrial metabolic activity, membrane potential and antioxidant bioavailability [62, 89]. Similarly, taxane treatment of rat and human DRG neurons lowered the resting and threshold membrane potential and increased the frequency of ectopic spontaneous activity [90]. In experimental models, paclitaxel increased the expression of voltage-gated calcium channels ( $\text{Ca}_v$ ) 3.2 and calcium current amplitude and decreased the excitability threshold of dorsal root sensory neurons, which when inhibited decreased mechanical hypersensitivity [87, 91, 92]. Further, toll-like receptor (TLR) 4 is also upregulated, resulting in increased intracellular calcium mediated by the co-located protein  $\text{Ca}_v$ 3.2. Moreover, paclitaxel increases the expression of Nav 1.7 channels in a dose-



**Fig. 1** The current hypothesis for the pathogenesis of OIPN. Accumulation of oxaliplatin occurs in dorsal root ganglion neurons, where it interferes with DNA and mtDNA cross-linking. This results in a direct dose-dependent toxicity of DRG neurons and neuronal mitochondria. There is a subsequent decrease in mitochondrial respiration and ATP. The resultant oxidative stress contributes to disruption in DNA and mtDNA replication and transcription, leading to diminished energy status and increased neuronal apoptosis. Increased production of ROS together with activation of astrocytes causes the release of pro-inflammatory mediators TNF- $\alpha$  and IL-1 $\beta$  and decreased expression of cytokines IL-10 and IL-4 with a neuroprotective function. Subsequently, leucocytes are activated and travel down a chemotactic gradient to the dorsal root ganglion and peripheral nerves, leading to neuroinflammation. Neuroinflammation and ROS cause damage to dorsal root ganglion neurons, leading to apoptosis, which contributes to calcium dysregulation,

dependent manner in human DRG neurons in culture, leading to increased ectopic spontaneous activity [92, 93]. Notably, paclitaxel can

axonal energy depletion and damage to neuronal organelles. Both ROS and neuroinflammation are implicated in nociceptor sensitisation, mechanical hyperalgesia and cold allodynia in preclinical models. Oxaliplatin interacts directly with VGKC, NaV channel, TRPM isoforms in sensory neurons contributing to cold hyperalgesia/allodynia and hyperexcitability of peripheral neurons. Further, a metabolite of oxaliplatin, oxalate chelates  $Ca^{2+}$  ions in the acute phase, contributing to neuronal excitability and increasing spontaneous activity of neurons. ATP: adenosine triphosphate,  $Ca^{2+}$ : calcium, DNA: deoxyribonucleic acid, DRG: dorsal root ganglion, NaV: voltage-gated sodium, OIPN: oxaliplatin-induced peripheral neuropathy, mtDNA: mitochondrial DNA, ROS: reactive oxygen species, IL-1B: interleukin 1B, IL-4: interleukin 4, IL-10: interleukin 10, TRPM: transient receptor potential melastatin, TNF- $\alpha$ : tumour necrosis factor- $\alpha$ , VGKC: voltage-gated potassium channel

bind and activate TLR4 on macrophages, engaging signalling pathways that lead to increased gene expression and release of nuclear

factor kappa B (NF- $\kappa$ B), initiating inflammatory and cytokine cascades [94]. TLR4, MyD88 and ERK1/2 expression is increased in IB4<sup>-</sup> and CGRP<sup>+</sup> DRG neurons [94–96]. Inflammatory mediators IL-6, IL-8, IL-10, monocyte chemoattractant protein-1 (MCP-1) and activated Langerhans cells are upregulated, where they propagate the further release of pro-inflammatory cytokines [97–99]. Furthermore, there is increased expression of stress and inflammatory markers in Schwann cells and lumbar DRG neurons [100, 101]. Activation and migration of CD68<sup>+</sup> macrophages, CD8<sup>+</sup> T cells and CD11b<sup>+</sup> leucocytes towards the DRG and peripheral nerves has been identified [99–101]. Thus, sensitisation of C-fibres, net energy loss, neuroinflammation and hyperexcitability contribute to paclitaxel-induced peripheral neuropathy. The hypotheses of the pathomechanism of TIPN is summarised in Fig. 2.

## VINCA ALKALOIDS

Vinca alkaloids are natural (vincristine and vinblastine) and semi-synthetic (vindesine and vinorelbine) chemotherapeutics derived from the periwinkle plant and are used either alone or in combination therapy to treat haematological malignancies, testicular cancer, myeloma, sarcoma, non-small cell lung cancer and tumours of the kidney, liver, lung, brain and breast [102]. Vincristine is arguably the most neurotoxic vinca alkaloid, with a majority of patients developing vincristine-induced neuropathy (VIPN) [10, 103], the severity of which is dose-dependent [104]105. Genetic polymorphisms in genes associated with Charcot-Marie-Tooth (CMT) disease appear to increase the risk of VIPN [106]. The incidence of VIPN or vinorelbine-induced neuropathy leading to sensory neuropathy is ~ 20%, with motor impairment in 17.5% of adult patients [107, 108]. The most common presentation of VIPN is a length-dependent sensory neuropathy, with significant motor impairment and occasional cranial nerve involvement [107]. Surprisingly, 91% of patients reported continuing symptoms 12 months after cessation of

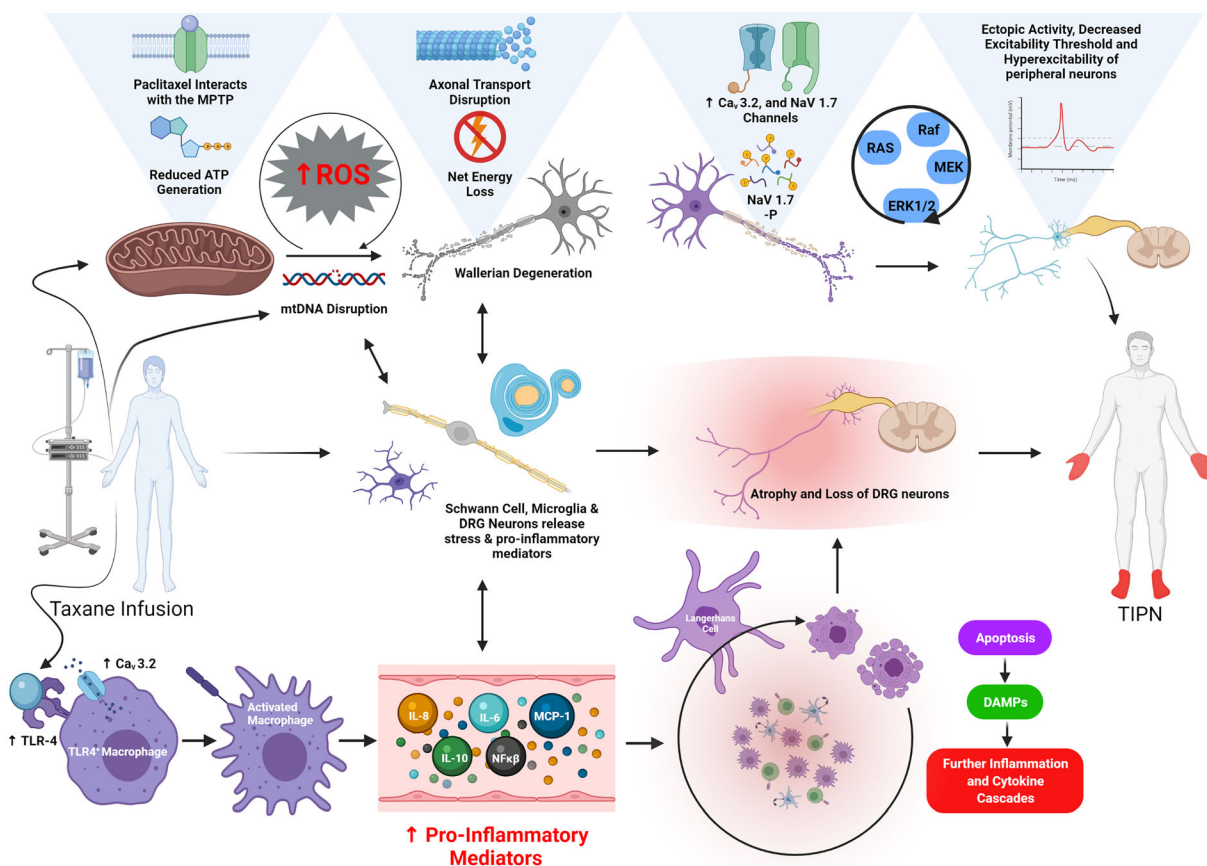
treatment [109], and there is evidence for long-term distal sensory [107, 110] and motor deficits in vincristine-treated cancer survivors [30].

## PATHOGENESIS OF VIPN

Anterograde transport of organelles and membrane proteins and retrograde transport of signalling molecules depends on microtubule-based transport [88]. Vinca alkaloids interfere with and disrupt microtubule assembly and mitotic spindle formation [111, 112]. They also increase the stability of microtubules, which impacts negatively on the ability of the cell to dynamically alter the structure of the cytoskeleton affecting axonal transport [88] 113. Additionally, vincristine is mitotoxic and can impair the mitochondrial electron transport chain, resulting in defective energy production [114]. Axonal degeneration requires both sterile alpha and TIR motif-containing proteins SARM1 and MAPK, and the deletion of SARM1 protects mice from developing VIPN [115]. Other intracellular targets include the NF-E2-related factor and haeme oxygenase 1/carbon monoxide system (Nrf2/HO-1/CO) which modulates the expression of connexin 43 (Cx43), protecting against nerve damage and reducing vincristine-induced neuroinflammation [116]. Increased expression of inflammatory markers TNF- $\alpha$  and IL-1 $\beta$  and increased expression of TRPA1 were recently identified in models of VIPN [117]. Moreover, mRNA gene ontology has identified the inflammatory role of vincristine on microglia and upregulation of pro-inflammatory genes including frizzled-related protein 2 (SFRP2) and C-X-C motif chemokines (CXCL) 10 and 9 [118]. The current available data on the hypothesised mechanism of VIPN is shown in Fig. 3A.

## THALIDOMIDE-INDUCED PERIPHERAL NEUROPATHY

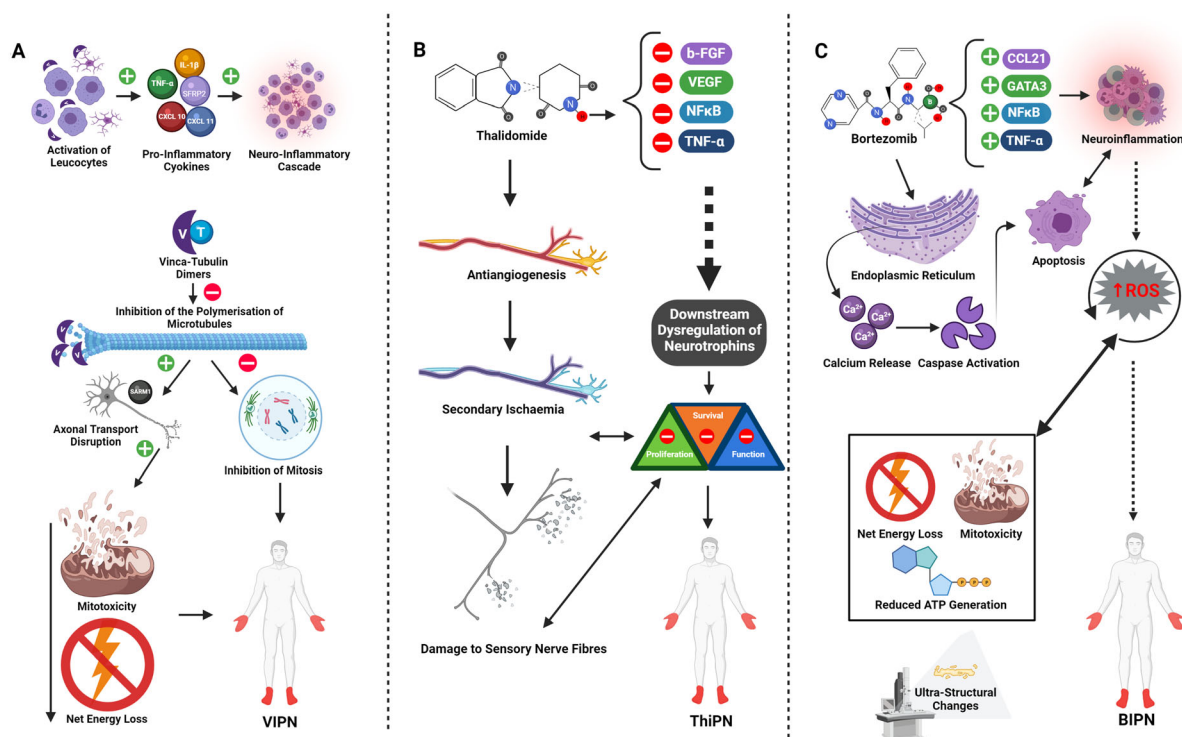
Thalidomide is a US Food and Drug Administration (FDA)-approved treatment for multiple myeloma (MM) [119]. Patients treated with thalidomide for MM, glioblastoma, renal cell



**Fig. 2** The current hypothesis for the pathogenesis of TIPN. Taxanes such as paclitaxel directly interact with TLR-4 on macrophages. This interaction upregulates the expression of TLR-4 and activates macrophages leading to the release of NF-κB, leading to further downstream pro-inflammatory cascades. Activated Langerhans cells release IL-6, IL-8, IL-10 and MCP-1. Subsequently, there is activation and migration of macrophages, cytotoxic T-cells, monocytes and neutrophils towards the DRG and peripheral nerves. DRG neurons and IB4-/GCRP+ peripheral fibres increase expression of inflammatory associated markers such as TLR4, MyD88 and ERK1/2. Similarly, inflammatory signalling is increased in Schwann cells, microglia and DRG neurons together with markers of cellular stress. Oxidative stress and the generation of ROS further impacts upon mitochondrial performance, limits intracellular energy stores of peripheral neurons and contributes to inflammation and intracellular damage. Further, taxanes such as paclitaxel interact with the MPTP, which culminates in a reduction in ATP generation and

mitochondrial generation. Taxanes disrupt microtubule polymerisation and impair the function of the axonal microtubule network. The expression of CaV 3.2 and NaV 1.7 are upregulated after treatment with taxanes, resulting in changes to the excitability threshold of peripheral neurons. The sensitisation of peripheral neurons and subsequent changes in neuronal excitability result in mechanical hypersensitivity and ectopic spontaneous activity which contribute to the development of TIPN. ATP: adenosine triphosphate, CaV: low voltage-activated T-type calcium channel, CGRP: calcitonin gene-related peptide, DAMP: damage-associated molecular pattern, DRG: dorsal root ganglion, ERK1/2: extracellular signal-regulated kinase, IB4: isolectin B4-binding glycoprotein, IL-6: interleukin 6, IL-8: interleukin 8, IL-10: interleukin 10, NaV: voltage-gated sodium, NF-κB: nuclear factor kappa B, MCP-1: monocyte chemoattractant protein-1, MEK: mitogen-activated protein kinase kinase, ROS: reactive oxygen species, TIPN: taxane-induced peripheral neuropathy, TLR-4: toll-like receptor 4





**Fig. 3** The current hypothesis for the pathogenesis of VIPN (A), ThiPN (B) and BIPN (C). A Vinca alkaloids such as vincristine activate leucocytes and microglia, causing the attraction and activation of downstream pro-inflammatory cytokines, leading to neuroinflammation. Vinca alkaloids inhibit the polymerisation of microtubules and therefore the formation of mitotic spindles causing disruption to axonal transport. This, together with mitotoxicity, causes net energy loss by impairing the electron transport chain. These mechanisms culminate in a distal sensorimotor axonal neuropathy. B Thalidomide inhibits VEGF, b-FGF, NF- $\kappa$ B and TNF- $\alpha$ , leading to dysregulation of neurotrophins. This impedes signalling responsible for the survival and proliferation of neurons. Further, antiangiogenic properties of thalidomide cause secondary ischaemia and hypoxia of small nerve fibres, leading to damage to sensory nerve fibres. C Bortezomib causes the release of intracellular calcium from the endoplasmic reticulum in sensory neurons, leading to caspase activation and subsequent cellular apoptosis. Pro-

inflammatory mediators are upregulated after treatment with bortezomib, leading to further cytokine signalling cascades and neuroinflammation. Bortezomib is mitotoxic, leading to damage to neuronal mitochondria, diminished respiration and reduced ATP production, culminating in neuronal energy failure. Further, oxidative stress and ROS contribute to intracellular damage to neuronal organelles (including mitochondria) and apoptotic mechanisms. Ultrastructural changes are seen in the myelin sheath of neurons, although the contribution of these changes warrants further investigation. AT: adenosine triphosphate, b-FGF: basic fibroblast growth factor, Ca<sup>2+</sup> calcium, CCL21 -CXCL-9-C-X-C motif chemokine 9, CXCL-10-C-X-C motif chemokine 10, C-X-C motif chemokine 21, IL-1 $\beta$ : interleukin 1 $\beta$ , NF- $\kappa$ B: nuclear factor kappa B, SARM1: sterile alpha and TIR motif-containing 1, SFRP2: frizzled-related protein 2, TNF- $\alpha$ : tumour necrosis factor  $\alpha$ , VEGF: vascular endothelial growth factor

carcinoma, colorectal and lung, melanoma, and breast and prostate cancer can develop thalidomide-induced peripheral neuropathy (ThiPN) [32, 102, 120–122]. Symptoms include symmetrical numbness, tingling, burning pain and sensitivity to touch and heat, with

hyperaesthesia, hypoaesthesia and paraesthesia in a glove-and-stocking distribution [32] with tremor, muscle cramps, distal muscle weakness, areflexia, loss of proprioception, gait ataxia and/or a lack of coordination [32, 123–128]. The incidence of ThiPN ranges from 11 to 75% and



is dependent on dose [120, 122, 129–134] and duration of exposure [125]. As such, the results of phase I studies giving thalidomide to the maximum tolerable dose are not representative of patients who are receiving this medication over a longer duration. Peripheral neuropathy induced by the thalidomide analogues lenalidomide and pomalidomide are less severe and occur at a lower incidence [135–137], making them the agents of choice in those with pre-existing neuropathy. MM is currently incurable and requires long durations of exposure to thalidomide and its analogues, which results in accumulative chemotoxicity [138]. This is especially relevant as the 5-year relative survival rate of M has increased in recent years [139]. Barlogie et al. [140] reported that 90% of participants with a National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)  $\geq 2$  grade ThiPN improved to a grade  $\leq 2$  within 3–4 months of thalidomide dose attenuation. However, complete clinical recovery is limited to approximately one quarter of patients [124, 128, 141–143].

## PATHOGENESIS OF THIPN

The exact pathomechanism of thalidomide is yet to be fully elucidated, but antiangiogenic properties [144] may lead to hypoxia of small nerve fibres [145]. Additionally, the immunomodulatory action of thalidomide inhibits basic fibroblast growth factor (b-FGF), vascular endothelial growth factor (VEGF), TNF- $\alpha$  and NF- $\kappa$ B and dysregulates neurotrophins; the signalling molecules responsible for the proliferation, survival and function of neurons are shown in Fig. 3B [146]. Further, preclinical ThiPN animal models demonstrate improvement of NCS following the injection of VEGF [147].

## BORTEZOMIB

The proteasome inhibitors bortezomib, ixazomib and carfilzomib are FDA-approved treatments for MM [148, 149] and are used in the treatment of progressive, relapsed or refractory

MM and mantle cell lymphoma [150, 151]. Bortezomib-induced peripheral neuropathy (BIPN) is a distal, symmetrical, length-dependent axonal sensorimotor neuropathy characterised by mild to moderate sensory loss, mild to severe neuropathic pain and mild motor weakness of the distal lower extremities [[33, 152]. Phase II trials have identified a BIPN incidence of 31–37%, with grade  $\geq 2$  neuropathy present in 28% of participants [153–155]. Although ixazomib and carfilzomib have a lower incidence of CIPN [156–158], long-term treatment [159] with the addition of other chemotherapeutic agents [160] is required to maintain remission.

## PATHOGENESIS OF BIPN

Bortezomib initiates apoptosis through the release of intracellular  $\text{Ca}^{2+}$  in the endoplasmic reticulum, leading to activation of caspase, a protease enzyme essential for programmed cell death [161]. A study showed vacuolation of DRG-associated mitochondria [162], although these findings could not be replicated [163]. Bortezomib treatment increased the number of swollen and vacuolated mitochondria in A-fibres and C-fibres compared to controls, and mitochondrial respiration and adenosine triphosphate production were reduced, indicating cumulative energy failure as a pathogenic mechanism of BIPN [164]. In a recent study, bortezomib exhibited neurotoxicity in PC12 neuroblastoma cells through the induction of apoptosis which was ameliorated with antioxidants, implicating oxidative stress in the pathogenesis of BIPN [165]. Ultrastructural features of myelin sheath degeneration of large nerve fibres and axonal degeneration of C-fibres have been identified [162, 163]. Inhibition of NF- $\kappa$ B and TNF- $\alpha$  attenuates the severity of BIPN in preclinical models [166, 167]. Indeed, bortezomib treatment increases the expression of GATA-binding protein (GATA3), a transcription factor implicated in the regulation of inflammatory signalling cascades and upregulation of the T-cell chemoattractant chemokine C–C motif ligand 21 (CCL21) in dorsal horn neurons, which when silenced attenuates

mechanical allodynia in Sprague Dawley rats [168]. The current hypothesis for the pathomechanism of BIPN is summarised in Fig. 3C.

## DIAGNOSTIC METHODS

Electrodiagnostic methods are considered the reference standard for the functional assessment of large sensory and motor fibres which drive paraesthesia, numbness and weakness seen in people with CIPN. Although sensory testing used in composite scoring systems is often deployed in the clinical setting, a rigorous, lengthy battery of standardised sensory tests is required to reliably identify a patient's sensory phenotype. Further, these tests are subjective and cannot discriminate between a central or peripheral disease process of the somatosensory nervous system, and benefit from the addition of a structural measure of peripheral nerve fibres. In light of this, we include an overview of self-reported outcome measures, composite scoring systems, functional tests of large fibres, structural measure of small fibres such as skin biopsy, and highlight the novel, reiterative method of corneal confocal microscopy. This method is of particular interest, as the early detection of CIPN may enable health care professionals to determine subclinical nerve damage and assist in changes to dosing strategies before the neuropathy becomes irreversible. In this section we highlight the methods used to quantify CIPN in both clinical and research settings.

## IDENTIFICATION OF CIPN AND GRADING

The methods used in both clinical trials and medical practice to identify and grade the severity of CIPN can be broadly separated into instruments which utilise patient-reported outcomes, composite scoring systems with a functional assessment component, and quality-of-life tools [169]. Most commonly used is the clinician-led patient-reported tool, National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), although

other instruments such as the Eastern Cooperative Oncology Group (ECOG) criteria and the World Health Organization (WHO) neurotoxicity scale [170] are also used. The latest version of the NCI-CTCAE (version 5.0) (Table 3) grades both motor and sensory neuropathy according to asymptomatic (grade 1), moderate (grade 2), severe (grade 3) or life-threatening (grade 4) neurotoxicity. Composite scoring systems such as the Total Neuropathy Score (TNS) use patient-reported symptoms, physical examination, vibration perception threshold and nerve conduction studies to grade CIPN, although there are versions which omit vibration perception threshold (TNSr) and nerve conduction studies (TNSc) [169]. Further, the TNS clinical (TNSc) and nurse-administered TNS (TNSn) have been shown to correlate well with the emergence of sensory and motor symptoms after the completion of chemotherapy, identifying 88% of participants who developed CIPN [171].

Functional assessments are self-reported questionnaires measuring both the quality of life and symptoms specific to how neurotoxicity impairs activity. These measures are often tailored to the primary cancer such as the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-neurotoxicity (FACT/COG-Ntx) tool, which has been shown to correlate well with the TNSc and TNSn [171]. Other examples of functional assessments include the European Organisation for Research and Treatment of Cancer (EORTC) and the chemotherapy-induced peripheral neuropathy questionnaire (CIPN20). These instruments have been reviewed extensively by Cavaletti et al. [170] and Park et al. [169].

## NERVE CONDUCTION STUDIES (NCS)

NCS provide an objective measure of large fibre function and are considered the reference standard for the diagnosis of large fibre involvement in CIPN [172]. Peripheral nerve demyelination is accompanied by conduction slowing and latency prolongation, and axonal

**Table 3** The NCI-CTCAE grading system (version 5.0) [354]

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	Asymptomatic	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	–

*ADL* activities of daily living

loss is accompanied by a reduction in amplitude.

In patients treated with paclitaxel and oxaliplatin, NCS can be used to confirm a symmetric, length-dependent, predominantly sensory distal neuropathy [173–177]. However, in acute OIPN there are rarely significant changes in NCS, although motor axons can develop increased refractoriness resulting in repetitive motor discharges [173, 178, 179]. Further, a change in sensory excitability in acute OIPN predicts the development of chronic OIPN, a purely sensory neuropathy with a reduction in sensory sural nerve action potential (SNAP) and nerve conduction velocity (SNCV) without motor NCS involvement [180]. In a longitudinal study of ten participants, the phenomenon of coasting was evidenced by worsening median and sural sensory amplitudes at least 3 months after completing oxaliplatin-based chemotherapy [181]. The typical presentation of TIPN is that of a predominantly distal sensory axonal neuropathy with some motor involvement [172, 182]. A recent longitudinal study identified significantly reduced SNAP amplitudes predominantly in the upper limbs, but to a lesser extent in the lower limbs, 12 months after completion of taxane chemotherapy, arguing for a non-length-dependent effect [15]. Both acute and chronic thalidomide neurotoxicity are characterised by attenuation of median, radial and sural SNAPs and compound muscle action potentials (cMAPs) of the peroneal and tibial nerves [126]. NCS in patients with BIPN largely indicate a predominantly small fibre sensory axonal

neuropathy, with less frequent motor neuropathy [129]. Bortezomib and thalidomide combination therapy is associated with a significant reduction in sural SNAP, peroneal motor nerve action potential (PMNAP) and peroneal motor nerve conduction velocity (PMNCV) [33, 127]. NCS in people with VIPN is characterised by a distal sensorimotor axonal neuropathy and motor involvement [172], with prolongation of distal latencies but preserved conduction velocities [183]. Furthermore, NCS parameters may deteriorate before or after the development of neuropathic symptoms [47, 127, 129, 172, 184–187].

## QUANTITATIVE SENSORY TESTING (QST)

QST provides an extensively validated mechanism-based and symptom-orientated approach to neuropathic pain. The loss of nerve fibre sensitivity or deafferentation can be detected using quantitative sensory testing for different nerve fibre populations. The loss of A $\beta$ -fibre sensitivity is indicated by impaired vibration perception, light touch or mechanical detection thresholds. C-fibre dysfunction is reflected by abnormal heat detection and heat pain thresholds, whilst A $\delta$ -fibre dysfunction is indicated by abnormal thresholds to pinprick stimuli, mechanical pain and cold detection [188–190]. The majority of patients with CIPN from a range of drugs exhibit reduced or absent pinprick and vibration perception thresholds and impaired proprioception [191]. Early impairment of

vibration detection and cold detection thresholds have been identified from week 12 of treatment with oxaliplatin, with an increase in mechanical detection thresholds 6 months after finishing treatment [180, 192]. Cold pain threshold can be used to dichotomise participants with acute OIPN and change over time [193]. People with TIPN exhibit diminished tactile perception in the upper and lower extremities, with worsening VPT in the lower limbs [194]. Participants with VIPN and BIPN exhibit widespread abnormalities in touch detection, pinprick detection and heat detection thresholds both within and outside self-reported areas of involvement [195, 196].

## SKIN BIOPSY

The accepted gold standard for diagnosing small fibre pathology is skin biopsy [197, 198]. Normative age- and sex-related values for intraepidermal nerve fibre density have been published for clinical use [199]. In preclinical models of paclitaxel- and vincristine-induced peripheral neuropathy, there is a significant reduction in intraepidermal nerve fibres [91, 98]. Indeed, a significant decrease in intraepidermal nerve fibre density (IENFD) at the distal leg was identified in eight patients 6 months after oxaliplatin treatment had been stopped [200]. Notably, a recent study found a significant time-dependent decrease in IENFD 6 months after treatment had been stopped [180]. In patients with BIPN, whilst epidermal nerve density did not differ, there was a reduction in subepidermal nerve fibre density [201]. Further work is needed to characterise the differential effect of different chemotherapy drugs on small nerve fibres in the skin.

## CORNEAL CONFOCAL MICROSCOPY

Corneal confocal microscopy (CCM) is a non-invasive, reiterative ophthalmic imaging technique that detects small nerve fibre abnormalities in the subbasal nerve plexus in a range of peripheral neuropathies [202–210]. A large body

of published data shows that CCM has good diagnostic [211] and prognostic [212] utility in diabetic neuropathy. Recently, CCM has been proposed to have utility in the diagnosis and follow-up of patients with CIPN [213].

In an early study of 15 patients with colorectal cancer treated with oxaliplatin, 10 patients developed a significant worsening of TNSc and 8 patients developed NCV evidence of a sensory axonal neuropathy [214]. CCM demonstrated a significant abnormality in 10/15 patients characterised by a reduction in corneal nerve fibre density (40%) and length (37%). Interestingly, after receiving the final cycle of chemotherapy, two patients with normal clinical and neurophysiological findings had evidence of severe corneal nerve loss, and 3 weeks later they developed neuropathic symptoms, indicative of coasting [214]. In 21 patients with gastro-oesophageal cancer without neuropathic symptoms there was evidence of corneal nerve loss which correlated with the stage of cancer. After three cycles of platinum-based chemotherapy, 61.5% of patients developed grade 1 symptomatic paraesthesia on CTCAE criteria; however, all patients except those with metastatic liver disease showed an increase in corneal nerve fibre length [205]. CCM has also shown a significant reduction in corneal nerve fibre density, length and beading in patients with MM undergoing treatment with bortezomib, despite clinically evident neuropathy being present in only 38.5% of patients [215]. More recently, of 63 patients who had received docetaxel for breast cancer ( $n = 28$ ) or oxaliplatin for colorectal cancer ( $n = 35$ ) 5 years prior to detailed neuropathy phenotyping, 41.3% still had evidence of CIPN, of whom 58% had pure large fibre neuropathy based on NCS [216]. Detailed QST revealed increased cold, warm, mechanical and vibration detection thresholds with no evidence of pinprick hyperalgesia or dynamic mechanical, cold or warm allodynia. CCM demonstrated no significant difference in corneal nerve fiber length, density or branch density between controls and patients with CIPN with and without small fibre neuropathy [216]. In a study comparing CCM in different peripheral neuropathies, patients with CIPN had evidence of corneal nerve fibre loss in

a distinct pattern based on the corneal nerve fractal dimension, which differed from patients with diabetic neuropathy or chronic inflammatory demyelinating neuropathy [217]. A study of 70 patients with breast, colorectal, upper gastrointestinal and gynaecological cancer having received either paclitaxel ( $n = 40$ ) or oxaliplatin ( $n = 30$ ) within the past 3 to 24 months showed evidence of a significant reduction in the corneal nerve fibre and inferior whorl lengths [218]. Furthermore, corneal nerve fiber length, inferior whorl length, average nerve fiber length and corneal nerve fiber density were significantly lower in patients with neuropathy compared to those without neuropathy based on the correlation of TNSr and inferior whorl length with hand dexterity [218]. These data suggest that CCM may have diagnostic and prognostic value in CIPN.

## CHEMOTHERAPY AND NEUROPATHIC PAIN

A large meta-analysis of 13,683 people with CIPN estimated the prevalence of neuropathic pain to be as high as 40% [219]. A recent international study of 2003 patients with CIPN has found a similar prevalence of neuropathic pain, which significantly impacted upon quality of life and daily functioning [220]. CIPN is predominantly a sensory neuropathy, as summarised in Table 2, with pain being the most bothersome symptom [221]. Indeed, the symptom burden of CIPN including sensory disturbances and neuropathic pain profoundly impacts on the quality of life of survivors of cancer [84, 191, 222–227]. CIPN also affects functionality and the capacity to work both during and after treatment, fuelling unemployment and loss of working time [228]. Moreover, a recent US administrative claims analysis by Song et al. [229] found that individuals with painful CIPN incur a significant economic burden driven by costs of analgesic drug prescriptions, increased rates of hospitalisation, emergency department visits and outpatient hospital visits compared to participants treated for cancer who did not develop CIPN. Pike et al. [230] showed that painful CIPN was associated

with higher average costs of \$17,344 compared to patients without CIPN. Notably, oxaliplatin- or paclitaxel-based chemotherapy regimens are more likely to result in neuropathic pain, and the pain associated with OIPN and TIPN is more severe and protracted [15]. The treatment of chronic neuropathic pain is often inadequate and may be poorly tolerated [231].

## PREVENTATIVE TREATMENT

A Cochrane systematic review of interventions and an expert group systematic review by the American Society of Clinical Oncology (ASCO) recommended against the use of a range of interventions (acupuncture, cryotherapy, exercise therapy or ganglioside-monosialic acid (GM-1), retinoic acid, amifostine, amitriptyline, calcium magnesium infusion (Ca/Mg), calmagofodipir, cannabinoids, carbamazepine, L-carnosine, diethyldithiocarbamate (DDTC), gabapentin, pregabalin, glutamate, glutathione, goshajinkigan (GJG), metformin minocycline, N-acetylcysteine, nimodipine, omega-3 fatty acids, ORG 2766, oxcarbazepine, recombinant human leukemia inhibitory factor, venlafaxine, vitamin B or vitamin E) in CIPN [232, 233]. Moreover, acetyl-L-carnitine is strongly advised against due to high-quality evidence indicating worsening neuropathy [232, 234].

The ACTION [Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks]/CONCEPT [Clinical Endpoints and Procedures for Peripheral Neuropathy Trials] consortia developed recommendations for CIPN prevention studies [235]. These included the selection of outcome measures and endpoints, eligibility criteria, potential effects of the investigational therapy on the efficacy of chemotherapy and accurate sample size estimation [235]. Summaries of studies evaluating putative preventative therapies are detailed in Table 4.

## NUTRACEUTICALS

Nutraceuticals as neuroprotective agents have not yielded strong evidence for the prevention



**Table 4** Treatments which require further validation or are not currently recommended for the treatment or prevention of chemotherapy-induced peripheral neuropathy

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
$\alpha$ -Lipoic acid	Gedlicka et al. 2002 [353]: Pilot study	Total ( $n = 15$ )	Oxaliplatin, raltitrexed	53% of participants developed less severe OIPN symptoms	No control group, small sample population. High-dose $\alpha$ -lipoic acid associated with nausea and gastric pain
$\alpha$ -Lipoic acid	Gedlicka et al. 2003 [354]: Pilot study	Total ( $n = 14$ )	Docetaxel, cisplatin	Six participants improved CIPN symptoms by at least one WHO grade score. Seven participants with severe CIPN did not respond to treatment	No control group, small sample population
$\alpha$ -Lipoic acid	Guo et al. 2014 [236]: Randomised, double-blind, placebo-controlled trial	Participants randomised ( $n = 243$ ) to $\alpha$ -lipoic acid ( $n = 122$ ) or placebo ( $n = 121$ ). Participants who did not complete the 24-week treatment were: $\alpha$ -lipoic acid ( $n = 88$ ) and placebo ( $n = 85$ ), leaving a final total ( $n = 173$ ) for analysis of: $\alpha$ -lipoic acid ( $n = 88$ ) placebo ( $n = 85$ )	Oxaliplatin, cisplatin	No statistically significant difference in FACT/GOG-Ntx scores between $\alpha$ -lipoic acid-treated or placebo-treated groups	High drop-out rate and poor $\alpha$ -lipoic acid treatment compliance

Table 4 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
OPERA ( $\alpha$ -lipoic acid, <i>Boswellia serrata</i> , methylsulfonylmethane, bromelain)	Desideri et al. 2017 [237]: Prospective study	Total ( $n = 25$ )	Cisplatin, carboplatin, vinca alkaloid, taxanes and eribulin	Changes identified in patient-reported pain scores after 12 weeks of therapy compared to baseline	No placebo, small sample size
Neuronorm (docosahexaenoic acid, $\alpha$ -lipoic acid, vitamin C and vitamin E)	Maschio et al. 2019 [355]: Phase II prospective study	Total ( $n = 31$ )	Bortezomib	12 participants reported no BIPN, with 13 participants progressing to painful BIPN (grade 1). Five participants developed BIPN grade $\geq 2$ , which is fewer than the proposed 40% expected by the primary end-point	No comparator group. Small sample size
ORG 2766	van der Hoop et al. 1990 [332]: Prospective study	Total ( $n = 67$ ) Placebo ( $n = 25$ ) Low-dose ORG 2766 ( $n = 22$ ) High-dose ORG 2766 ( $n = 20$ ) (Participants received either 4 or 6 cycles of chemotherapy)	Cisplatin	Vibration perception threshold after six cycles of cisplatin chemotherapy was preserved in the high-dose ORG 2766 group compared to placebo ( $5.87 \pm 1.97 \mu\text{m}$ vs $0.88 \pm 0.17 \mu\text{m}$ ; $p < 0.005$ )	-



**Table 4** continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
ORG 2766	Roberts et al. 1997 [356]: Randomised, multicentre, double-blind, placebo-controlled trial	Total ( <i>n</i> = 174) Placebo ( <i>n</i> = 67) ORG 2766 2 mg ( <i>n</i> = 63) ORG 2766 4 mg ( <i>n</i> = 66)	Cisplatin, cyclophosphamide	ORG 2766 increased the rate and severity of CisPN ( <i>p</i> < 0.05)	-
ORG 2766	Koepfen et al. 2004 [357]: Randomised, double-blind, placebo-controlled study	Total ( <i>n</i> = 147) ORG 2766 ( <i>n</i> = 73) Placebo ( <i>n</i> = 74)	Vincristine	No significant differences observed between placebo and ORG 2766 groups	-
ACL	Hershman et al. 2013 [234]: Randomised double-blind placebo-controlled Trial	Total ( <i>n</i> = 409) ALC ( <i>n</i> = 201) Placebo ( <i>n</i> = 194)	Paclitaxel	ACL significantly worsened CIPN symptoms after 24 weeks	-
Curcumin	Howells et al. 2019 [238]: Randomised, standard-of-care comparator study	Total ( <i>n</i> = 27) FOLFOX ( <i>n</i> = 9) FOLFOX + curcumin ( <i>n</i> = 18)	Oxaliplatin	No significant difference between treatment arms in OIPN	-

Table 4 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Venlafaxine (prevention)	Zimmerman et al. 2016 [297]: Pilot, randomised, placebo-controlled, double-blind study	Total ( $n = 43$ ) Venlafaxine ( $n = 22$ ) Placebo ( $n = 21$ )	Oxaliplatin	No significant effect of venlafaxine in the prevention of acute or chronic OIPN	OINS scores indicated improvement in cold hyperalgesia of the throat
Glutamine (prevention)	Wang et al. 2007 [247]: Randomised, standard-of-care-controlled trial	Total ( $n = 86$ ) Glutamine ( $n = 42$ ) Control ( $n = 44$ )	Oxaliplatin, 5-FU	The incidence of acute OIPN was lower in the glutamine group compared to the control group (33.3% vs 56.8%; $p = 0.03$ )	No difference in NCS abnormalities ( $p = NS$ )
Glutamine (prevention)	Vahdat et al. 2001 [248]: Non-randomised, standard-of-care-controlled trial	Total ( $n = 55$ ) Glutamine ( $n = 12$ ) Control ( $n = 33$ )	Paclitaxel	Significant reduction in TTPN severity such as dysaesthesia ( $p < 0.05$ ), motor weakness ( $p = 0.04$ ) and interference with daily functioning ( $p < 0.001$ )	No objective nerve function measures
Glutamine (prevention)	Stubblefield et al. 2005 [249]: Non-randomised, standard-of-care-controlled trial	Total ( $n = 36$ ) Glutamine ( $n = 12$ ) Control ( $n = 24$ )	Paclitaxel	The glutamine group reported lower incidence of weakness ( $p = 0.02$ ), vibration perception ( $p = 0.02$ ) and numbness ( $p = 0.004$ ) compared to controls	No difference in NCS abnormalities ( $p = NS$ )

**Table 4** continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Glutathione (prevention)	Cascinu et al. 1995 [245]: Randomised, placebo-controlled, double-blind trial	Total ( <i>n</i> = 43) Glutathione ( <i>n</i> = 25) Placebo ( <i>n</i> = 18)	Cisplatin	After 15 weeks, glutathione resulted in fewer incidents of clinically confirmed CisPN compared to the placebo group (16% vs 88%; <i>p</i> = 0.0001)	-
Glutathione (prevention)	Cascinu et al. 2002 [244]: Randomised, placebo-controlled, double-blind trial	Total ( <i>n</i> = 40) Glutathione ( <i>n</i> = 21) Placebo ( <i>n</i> = 19)	Oxaliplatin	Fewer participants developed grade 2–4 OIPN in the glutathione group compared to placebo ( <i>p</i> = 0.004)	-
Vitamin E (prevention)	Pace et al. 2003 [240]: Randomised, standard-of-care-controlled trial	Total ( <i>n</i> = 27) Vitamin E + cisplatin ( <i>n</i> = 13) Cisplatin alone ( <i>n</i> = 14)	Cisplatin	The incidence of CisPN was lower in the vitamin E-supplemented group compared to standard of care (30.7% vs 85.7%; <i>p</i> < 0.01)	No objective nerve function measures. Not placebo- or active-comparator-controlled
Vitamin E (prevention)	Pace et al. 2007 [241]: Multicentre randomised, placebo-controlled, double blind trial	Total ( <i>n</i> = 25) Vitamin E + cisplatin ( <i>n</i> = 11) Cisplatin alone ( <i>n</i> = 14)	Cisplatin	Preliminary analysis of the first 25 eligible participants indicated median difference between vitamin E and placebo groups ( <i>p</i> < 0.05)	-

Table 4 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Vitamin E (prevention)	Kottschade et al. 2011 [242]: Randomised, placebo-controlled, double blind phase III trial	Total ( <i>n</i> = 185) Vitamin E ( <i>n</i> = 94) Placebo ( <i>n</i> = 91)	Taxanes and platinum	No significant effect of vitamin E in the prevention of sensory CIPN	-
Vitamin E (prevention)	Argyriou et al. 2005 [243]: Pilot, randomised, standard-of-care-controlled, open-label, single-blind trial	Total ( <i>n</i> = 31) Vitamin E ( <i>n</i> = 16) Control ( <i>n</i> = 15)	Cisplatin, paclitaxel	CIPN incidence was reduced in the vitamin E group compared to controls (25% vs 73.3%; <i>p</i> = 0.019). NDS scores were lower in participants treated with vitamin E compared to controls (3.4 ± 6.3 vs 11.5 ± 10.6; <i>p</i> = 0.026)	-
Glutathione (prevention)	Milla et al. 2009 [358]: Randomised, placebo-controlled phase I trial	Total ( <i>n</i> = 27) Glutathione ( <i>n</i> = 14) Placebo ( <i>n</i> = 13)	Oxaliplatin	Grade 1–2 OIPN occurred in 50% of participants compared to 69% of participants treated with placebo ( <i>p</i> = 0.0037)	-

**Table 4** continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Calcium and magnesium (prevention)	Loprinzi et al. 2014 [258]: Randomised, placebo-controlled, double-blind phase III trial	Total ( <i>n</i> = 353) Calcium and magnesium infusion before and after chemotherapy ( <i>n</i> = 118) Calcium and magnesium infusion before and placebo after chemotherapy ( <i>n</i> = 116) Placebo ( <i>n</i> = 119)	Oxaliplatin	No significant effect of calcium magnesium infusion in the prevention of acute OIPN	-
Calcium and magnesium (prevention)	Knijn et al. 2011 [254]: Retrospective analysis of a randomised, standard-of-care-controlled phase III trial	Total ( <i>n</i> = 732) Calcium and magnesium ( <i>n</i> = 551) Standard-of-care ( <i>n</i> = 181)	Oxaliplatin	Incidence of OIPN (all grades) was reduced in the calcium and magnesium group compared to controls (85% vs 92%; <i>p</i> = 0.02). Incidence of $\geq 2$ OIPN was similarly reduced (40% vs 45%; <i>p</i> = 0.22)	-
Calcium and magnesium (prevention)	Han et al. 2013 [259]: Prospective randomised, placebo-controlled, double-blind phase I, crossover trial	Total ( <i>n</i> = 19) Calcium and magnesium ( <i>n</i> = 10) Placebo ( <i>n</i> = 9)	Oxaliplatin	No significant difference in self-reported acute OIPN symptoms	NCS abnormalities higher in calcium and magnesium compared to controls ( <i>p</i> = ns)

Table 4 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Calcium and magnesium (prevention)	Gamelin et al. 2004 [255]: Retrospective analysis of a cohort study	Total ( $n = 161$ ) Calcium and magnesium ( $n = 96$ ) Standard-of-care ( $n = 65$ )	Oxaliplatin	At the end of treatment all grade OIPN was reduced in the calcium and magnesium compared to standard of care (4% vs 31%; $p < 0.001$ ). (20% vs 45%; $p = 0.003$ ). OIPN severity (grade $\geq 3$ ) occurred at a lower incidence in participants treated with calcium and magnesium compared to standard of care (7% vs 26%; $p = 0.001$ )	–
Calcium and magnesium (prevention)	Ao et al. 2012 [256]: Meta-analysis	Total ( $n = 202$ )	Oxaliplatin	Fixed effects model identified calcium and magnesium has no effect on acute OIPN (OR = 0.41, 95% CI 0.11–1.49; $p = 0.70$ , $I^2$ , 0)	–
Amifostine (prevention)	Leong et al. 2003 [250]: Randomised, placebo-controlled, double-blind trial	Total ( $n = 58$ ) Amifostine ( $n = 21$ ) Placebo ( $n = 27$ )	Paclitaxel and carboplatin	No significant difference in neuropathy incidence of amifostine treatment between groups was identified	–

**Table 4** continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Amifostine (prevention)	Hilpert et al. 2005 [251]: Randomised, placebo-controlled, double-blind phase II trial	Total ( <i>n</i> = 72) Amifostine ( <i>n</i> = 37) Placebo ( <i>n</i> = 34)	Paclitaxel, carboplatin and epirubicin	Amifostine improved self-reported sensory CIPN symptoms (NCI-CTC) compared to controls ( <i>p</i> = 0.0046)	Amifostine caused worsening of nausea ( <i>p</i> = 0.0005) and vomiting ( <i>p</i> = 0.0083)
Amifostine (Ages 3–21) (prevention)	Gurney et al. 2014 [252]: Cohort study	Total ( <i>n</i> = 379) Average-risk ( <i>n</i> = 263) High-risk ( <i>n</i> = 116)	Cisplatin	Participants with average risk of hearing loss reduced the risk of hearing loss (OR, 0.30; 95% CI: 0.14–0.64). High risk participants did not prevent hearing loss (OR, 0.89; 95% CI: 0.31–2.54)	–
DDTC	Gandara et al. 1995 [253]: Randomised placebo-controlled multicentre trial	Total ( <i>n</i> = 214) DDTC ( <i>n</i> = 106) Placebo ( <i>n</i> = 108)	Cisplatin	Participants receiving DDTC with lower cumulative doses of cisplatin were more likely to cease chemotherapy treatment	–
Massage (prevention)	Izgu et al. 2019 [359]: Randomised, standard-of-care-controlled trial	Total ( <i>n</i> = 40) Massage ( <i>n</i> = 19) Control ( <i>n</i> = 21)	Paclitaxel	Reduced pain reported by massage group compared to controls at week 12 ( <i>p</i> < 0.05)	–



Table 4 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Electro-acupuncture (prevention)	Greenlee et al. 2016 [360]: Randomised sham-controlled pilot trial	Total ( $n = 48$ ) Electro-acupuncture ( $n = 25$ ) Sham electro-acupuncture ( $n = 23$ )	Paclitaxel, oxaliplatin	No difference between groups. Also, participants in receipt of electro-acupuncture recovered at a slower rate after chemotherapy treatment stopped	-
Calmangafodipir (prevention)	Glimelius et al. 2018 [361]: Randomised, placebo-controlled, double-blind phase II trial	Total ( $n = 173$ ) Placebo ( $n = 60$ ) Calmangafodipir ( $n = 113$ )	Oxaliplatin	Participants treated with calmangafodipir reported fewer sensory symptoms ( $p < 0.01$ ) and fewer incidents of physician-graded OIPN ( $p = 0.016$ ) compared to controls	Due to promising results, currently ongoing phase III trials
Pregabalin (prevention)	de Andrade et al. 2017 [283]: Randomised, placebo-controlled, double-blind phase II trial	Total ( $n = 143$ ) Pregabalin ( $n = 78$ ) Placebo ( $n = 65$ )	Oxaliplatin	Pregabalin did not decrease the incidence of chronic OIPN or neuropathic pain compared to placebo ( $p = NS$ )	-
Oxcarbazepine (prevention)	Argyriou et al. 2006 [362]: Randomised, open-label, standard-of-care-controlled trial	Total ( $n = 40$ ) Oxcarbazepine ( $n = 20$ ) Control ( $n = 20$ )	Oxaliplatin	The incidence of OIPN was reduced in the oxcarbazepine group compared to controls (31.2% vs 75%; $p = 0.033$ )	-

**Table 4** continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Carbamazepine (treatment)	Wilson et al. 2002 [363]: Phase I trial	Total ( <i>n</i> = 12)	Oxaliplatin	No impact on the symptoms or impaired NCS of OIPN	Small, non-randomised trial
Exercise (treatment)	Kleckner et al. 2018 [269]: Secondary analysis of multicentre, randomised, standard-of-care-controlled phase III trial	Total ( <i>n</i> = 355) Exercise ( <i>n</i> = 170) Control ( <i>n</i> = 185)	Taxanes, platinumums and vinca alkaloids	Exercise reduced self-reported sensory CIPN symptoms of thermal sensation in the hands or feet ( <i>p</i> = 0.045), paraesthesia ( <i>p</i> = 0.061) which was more pronounced in older ( <i>p</i> = 0.086), male ( <i>p</i> = 0.028) or participants with breast cancer ( <i>p</i> = 0.076)	-
Aromatherapy massage (treatment)	Izgu et al. 2019 [364]: Randomised, standard-of-care-controlled trial	Total ( <i>n</i> = 46) Massage ( <i>n</i> = 22) Control ( <i>n</i> = 24)	Oxaliplatin	Reduction in self-reported painful OIPN symptoms at week 6 in treated participants compared to standard of care	-

Table 4 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Acupuncture (treatment)	Molassiotis et al. 2019 [365]: Randomised, single-blind, standard-of-care-controlled trial	Total ( $n = 87$ ) Acupuncture ( $n = 44$ ) Control ( $n = 43$ )	Platinum, taxane, bortezomib	TNS scores improved after 20 weeks of treatment in participants treated with acupuncture compared to standard of care ( $p < 0.05$ ). Sensory NCI-CTC-AE scores improved ( $p < 0.05$ ) but not the motor subset items	–
Laser-acupuncture (treatment)	Hsieh et al. 2016 [267]: Prospective cohort study	Total ( $n = 17$ )	Oxaliplatin	Laser acupuncture reduced the severity of OIPN symptoms in both the hands and feet of participants ( $p < 0.05$ )	–
Acupuncture and methylcobalamin (treatment)	Han et al. 2017 [264]: Randomised, methylcobalamin controlled, prospective study	Total ( $n = 98$ ) Acupuncture + methylcobalamin ( $n = 49$ ) Methylcobalamin alone ( $n = 49$ )	–	After 84 days both groups improved pain scores, with reduced pain scores in the acupuncture group ( $p < 0.01$ )	–
Electro-acupuncture (treatment)	Rostock et al. 2013 [265]: Randomised placebo-controlled trial	Total ( $n = 59$ ) Electro-acupuncture ( $n = 14$ ) Hydroelectric baths ( $n = 13$ ) Vitamin B ( $n = 15$ ) Placebo ( $n = 17$ )	–	Electro-acupuncture demonstrated a worse effect in the treatment of CIPN symptoms ( $0.8 \pm 1.2$ ), with a group difference of $-0.3$ (95% CI $-1.4$ to $0.8$ ; $p = 0.705$ )	–

**Table 4** continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Electro-acupuncture	Garcia et al. 2014 [268]: Pilot study	Total (n = 19)	Thalidomide, bortezomib	At weeks 9–13, pain severity, fine motor functioning and walking all improved according to FACT/GOG-Ntx scores. No improvements in NCS were identified	–
Lidocaine (treatment)	Van den Heuvel et al. 2017 [366]: Prospective case series	Total (n = 9)	Platinum, taxanes, capecitabine, cyclophosphamide, trastuzumab, cyclophosphamide, capecitabine, imatinib, bevacizumab, etoposide and cytarabine	A significant analgesic effect in 88% of patients ( $p = 0.01$ ). Pain reduction was maintained for 23 days in five participants	–
Lamotrigine	Rao et al. 2008 [367]: Randomised, double-blind, placebo-controlled phase III trial	Total (n = 131)	Paclitaxel, docetaxel, carboplatin, cisplatin, oxaliplatin, vincristine and vinblastine	No significant relief of CIPN symptoms identified using lamotrigine	–

Table 4 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Oral mucosal spray containing delta-9 tetrahydrocannabinol and cannabidiol (treatment)	Lynch et al. 2014 [368]: randomised, placebo-controlled crossover pilot study patients	Total ( <i>n</i> = 16)	Cisplatin, oxaliplatin, paclitaxel, vincristine	No significant relief of pain intensity in participants with CIPN	-
Topical amitriptyline and ketamine	Gewandter et al. 2014 [271]: Multicentre, randomised, placebo-controlled, double-blind phase III trial	Total ( <i>n</i> = 462)	Taxane, non-taxane	No significant difference in self-reported sensory CIPN symptoms using topical amitriptyline and ketamine compared to placebo ( <i>p</i> = NS)	Short 5-week study
Topical baclofen, amitriptyline and ketamine	Barton et al. 2011 [369]: Randomised, placebo-controlled, double-blind trial	Total ( <i>n</i> = 150)	Taxanes, platinum, vinca alkaloids and thalidomides	Improvement in sensory ( <i>p</i> = 0.053) and motor ( <i>p</i> = 0.021) subscales of the EORTC QLQ-CIPN20 in the topical baclofen, amitriptyline and ketamine group compared to controls	-

Table 4 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome(s)	Notes
Topical amitriptyline	Rossignol et al. 2019 [272]: open-label, non-comparative, uncontrolled, prospective pilot clinical trial	Total (n = 44)	Oxaliplatin, bortezomib, vinca alkaloids, lenalidomide, bendamustine	A reduction in pain score of at least 3 points was observed after 1 week in all participants. After 4 weeks, pain scores were reduced to 2 (p < 0.0001)	-
Topical menthol 1% (treatment)	Fallon et al. 2015 [370]: Prospective study	Total (n = 38)	Oxaliplatin, cisplatin, carboplatin, paclitaxel and bortezomib	82% of participants had improvement in pain scores (p < 0.001). Improvements in HADS scores and QST were also identified (p < 0.001)	-
Capsaicin 8% patch	Anand et al. 2019 [275]: single-centre, open-label, longitudinal study	Total (n = 16)	Bortezomib, platinum, and or taxane	Self-reported measures indicated reduced spontaneous pain (p = 0.02), touch-evoked pain (p = 0.03), cold-evoked pain (p = 0.03), neuropathic pain (p = 0.0007), and continuous (p = 0.01) and overall pain (p = 0.004)	Potential disease modification as IENFD identified regenerative nerve markers

5-FU Fluorouracil, CIPN Chemotherapy-induced peripheral neuropathy, DDTC Diethylthiocarbamate, EORTC QLQ-CIPN20 European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-CIPN twenty-item scale, FACT/GOG-Nx Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity, IENFD Intraepidermal nerve fibre density, OIPN Oxaliplatin-induced peripheral neuropathy, NCI-CTC-AE Common Terminology Criteria for Adverse Events, NS not significant, NCS Nerve conduction studies, TIPN Taxane-induced peripheral neuropathy

of neurotoxicity. For instance,  $\alpha$ -lipoic acid [236], OPERA [237], curcumin [238] and Neuronorm [239] have shown no benefit in randomised controlled trials despite positive findings in preclinical studies. Similarly, despite positive pilot studies, a large phase III trial did not demonstrate a significant neuroprotective effect of vitamin E and glutathione supplementation [240–243, 244, 245] [246]. However, in two randomised, standard-of-care-controlled trials and a smaller non-randomised standard-of-care-controlled trial, glutamine was associated with reduced incidence and severity of dysaesthesias, nerve conduction impairment and interference with daily functioning [247–249]. Amifostine demonstrated a clinically meaningful benefit for the prevention of sensory and auditory CIPN but was associated with worsening nausea and vomiting [250–252]. Patients administered diethyldithiocarbamate (DDTC), with lower cumulative doses of cisplatin, were more likely to withdraw from treatment due to CisPN-related adverse events [253]. Similarly, the hexapeptide analogue of ACTH, ORG 2766, increased the incidence of CIPN in a smaller cohort study [252]. Caution is advised with nutraceuticals and supplements with unproven efficacy.

## CALCIUM AND MAGNESIUM INFUSION

Retrospective studies of patients with advanced colorectal cancer treated with oxaliplatin found that calcium and magnesium infusion (Ca/Mg) significantly reduced the incidence of all-grade OIPN compared to 5-fluorouracil and leucovorin [254, 255]. Notably, a meta-analysis found that Ca/Mg treatment reduced the incidence of severe chronic OIPN (grade  $\geq 2$ ) (0.44 (95% CI 0.23–0.85;  $p = 0.01$ )) but does not reduce the incidence of acute OIPN (0.41 (95% CI 0.11–1.49;  $p = 0.18$ )) [256]. The reduction in acute OIPN incidence with Ca/Mg infusions has not been replicated in a phase I RCT and a large phase III RCT (Table 4) [257–259].

## SYMPTOMATIC TREATMENTS

Recently published ASCO guidelines indicate that duloxetine is the only currently recommended treatment; however, due to a lack of definitive efficacy, *no* recommendations can be made for exercise therapy, acupuncture, scrambler therapy, gabapentin, pregabalin, topical gel treatment (containing baclofen/amitriptyline plus/minus ketamine), tricyclic antidepressants or oral cannabinoids in the treatment of symptomatic CIPN [232]. Based on current clinical trial data (Table 5), larger, high-quality studies are needed to confirm efficacy and identify risks of treatment [9, 232, 235, 260, 261].

## ACUPUNCTURE

In a systematic review of acupuncture for the treatment of CIPN, two out of three trials found acupuncture to be effective in improving self-reported CIPN measures [262–264], but one trial found no benefit [265]. A recent systematic review identified 19 RCTs with 1174 patients and showed that acupuncture significantly improved not only pain but also, surprisingly, nerve conduction velocity [266]. Pilot studies of electro-acupuncture and laser acupuncture have shown improvements in self-reported measures and sensory testing in patients with chronic CIPN [267, 268].

## EXERCISE

A secondary analysis of a large phase III randomised controlled trial of non-pharmaceutical interventions in cancer patients found that exercise reduced sensory symptoms in participants with OIPN, TIPN or VIPN, especially in participants who were older, male or had breast cancer [269]. A recent systematic review and meta-analysis indicated that exercise interventions significantly improve CIPN symptoms, and a sensorimotor-based exercise intervention reduced CIPN-induced loss of postural stability [270].



**Table 5** Current evidence for recommended treatment for painful chemotherapy-induced peripheral neuropathy [232, 235, 261, 371–375]

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome	Guideline
Duloxetine	Yang et al. 2012 [291]: Open-label pilot study	30	Oxaliplatin	OIPN improved in 47.4% of participants by one grade, with 62.6% maintaining on a steady grade	ASCO, ONS, NCI
	Smith et al. 2013 [290]: Randomised, placebo-controlled, double-blind, phase III crossover trial	141	Paclitaxel, oxaliplatin	Duloxetine statistically significantly reduced average pain score after 5 weeks compared to placebo (1.06 [95% CI, 0.72–1.40] vs 0.34 [95% CI, 0.01–0.66]; $p = 0.003$ )	
	Hirayama et al. 2015 [292]: Randomised, vitamin B12-controlled, open-label crossover pilot trial	32	Oxaliplatin, paclitaxel, vincristine and bortezomib	Duloxetine changed pain scores pain ( $p = 0.04$ ) and numbness ( $p = 0.03$ ) compared to placebo	
	Otake et al. 2015 [376]: Retrospective cohort study	25	Paclitaxel, carboplatin, epirubicin	Duloxetine improved CIPN symptoms in 56% of participants	
	Farshchian et al. 2018 [294]: Randomised, placebo-controlled, double-blind trial	156	Taxane and platinum	Both duloxetine and venlafaxine reduced neuropathic pain and CIPN grade at week 4 compared to controls ( $p < 0.05$ ). Duloxetine was more effective compared to venlafaxine ( $p < 0.05$ )	

Table 5 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome	Guideline
Anti-depressants	Kus et al. 2016 [296]: Retrospective case-control study	199	Taxanes, platinum	An improvement of 75% in pain score was reported in 53.5%, 58.3% and 45.2% in the first three visits compared to 0% in the control group ( $p < 0.001$ )	ESMO, NCCN
	Özdoğan et al. 2004 [377]: Pilot study	12	Platinums, vinca alkaloids, 5-FU, etoposide	Reduced pain scores were statistically significant compared to baseline ( $p \leq 0.001$ ). Increase in drowsiness reported ( $p = 0.041$ )	
	Durand et al. 2005 [378]: Case study	2	Oxaliplatin	Anecdotal functional improvements reported	
	Durand et al. 2012 [295]: Randomised, double-blind, placebo-controlled phase III trial	42	Oxaliplatin	Pain relief reported at a higher frequency in participants treated with venlafaxine compared to controls (31.3% vs 5.3%; $p = 0.03$ )	
	Hammack et al. 2002 [284]: Randomised, double-blind, placebo-controlled, crossover trial	51	Cisplatin	No significant impact on CiSPN pain or paraesthesia severity from baseline	
	Kautio et al. 2008 [285]: Randomised, double-blind, placebo-controlled trial	33	Vinca alkaloids, platinum and taxanes	No significant impact on CIPN pain	

Table 5 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome	Guideline
Gabapentinoids	Mishra et al. 2012 [279]: Prospective, randomised, double-blind, placebo-controlled trial	120	-	Number of participants requiring morphine was significantly lower in the amitriptyline, gabapentin and pregabalin treatment groups compared to placebo (56.7%, 33.3% and 16.7% vs 100%). Pregabalin appeared to outperform gabapentin in reducing lancinating pain ( $p = 0.026$ ) and dysaesthesia ( $p = 0.021$ )	ESMO, ASCO, NCCN
	Rao et al. 2007 [282]: Randomised, double-blind, placebo-controlled, crossover, phase III trial	84	Paclitaxel, docetaxel, carboplatin, cisplatin, oxaliplatin, vincristine or vinblastine	No benefit identified in reducing pain scores in participants with CIPN	
	Tsavaris et al. 2008 [280]: Pilot study	110	Docetaxel, paclitaxel, vinorelbine, oxaliplatin,	Approximately half of participants had no response to gabapentin therapy, whilst the other half had a decrease in chemotherapy dose self-reported to be managed by gabapentin pharmacotherapy	
	Magnowska et al. 2018 [281]: Prospective study	61	Paclitaxel, carboplatin	Participants receiving gabapentin report improved symptoms ( $p = 0.027$ ), pain ( $p = 0.027$ ) and neurological deficit ( $p = 0.019$ )	
	Saif et al. 2010 [379]: Prospective study	23		Pregabalin pharmacotherapy improved OIPN severity by 1–2 grades in 48% of participants	

Table 5 continued

Treatment	Author and study design	Number of patients	Antineoplastic agent	Study outcome	Guideline
Opioids	Cartoni et al. 2012 [277]: Pilot study	46	Bortezomib	Reduction in the intensity and frequency of pain reported in 47.8% of participants after 2 weeks compared to baseline (mean numeric rating scale = 3.65; $p < 0.01$ )	ESMO, NCCN
	Kim et al. 2018 (276): Multicentre, interventional, single-arm phase IV study	66	Taxanes, epothilones, platinum, bortezomib, thalidomide, vinca alkaloid	A 21.4% reduction in pain score in participants at week 4 ( $1.29 \pm 1.84$ ; $p < 0.0001$ )	

ASCO American Society of Clinical Oncology, ESMO European Society for Medical Oncology, ONS Oncology Nursing Society, NCI National Cancer Institute, NCCN National Comprehensive Cancer Network

## TOPICAL THERAPIES

A large phase III randomised, placebo-controlled trial of participants with CIPN treated with topical 2% ketamine plus 4% amitriptyline showed no benefit on mean pain, numbness or tingling scores when compared to placebo ( $p = 0.363$ ) [271]. However, a pilot study of 44 participants with CIPN treated with topical 10% amitriptyline showed a five-point reduction in mean pain scores after 4 weeks ( $p < 0.0001$ ) [272].

## HIGH-STRENGTH CAPSAICIN PATCH

An in vitro study showed that oxaliplatin modulates the sensitivity of the capsaicin receptor (TRPV1) response through a secondary intracellular messenger [273]. In a single-centre study, the high-dose capsaicin 8% patch reduced pain by 84% in 18 participants with OIPN, 12 weeks after the patch was applied [274]. Similarly, a single-centre, open-label,

longitudinal study showed that the capsaicin 8% patch ameliorated neuropathic pain in 16 participants with chronic CIPN, with evidence of regeneration of intraepidermal nerve fibres, suggestive of initial degeneration due to capsaicin [275]. Indeed, the latest ASCO guidelines indicate that the efficacy of the high-dose 8% capsaicin patch should be further explored [232].

## OXYCODONE

In a multicentre, phase IV study, oxycodone and naloxone taken together with gabapentin ( $\geq 900$  mg/day) was found to decrease mean numeric rating scale pain scores from  $6.0 \pm 1.3$  to  $4.7 \pm 2.1$ , after 4 weeks ( $p = < 0.0001$ ) [276]. Similarly, treatment with controlled-release oxycodone reduced mean pain intensity from 7.6 to 1.3 at day 14 ( $p < 0.002$ ) [277]. However, close monitoring of long-term opioid therapy, particularly in combination with gabapentoids, is advised [278].

## GABAPENTINOIDS

A double-blind, randomised, placebo-controlled trial found pregabalin to be more effective than both gabapentin and amitriptyline in decreasing pain scores, with a morphine-sparing effect associated with pregabalin monotherapy [279]. A pilot study and a cohort study identified gabapentin as a potential treatment with improved self-reported measures of CIPN [280, 281]. Nevertheless, a randomised, double-blind, placebo-controlled, crossover, phase III trial ( $n = 115$ ) failed to show a significant change in the pain score with gabapentin in patients with CIPN [282]. Further, the preemptive administration of pregabalin did not decrease the risk of painful OIPN [283].

## TRICYCLIC ANTIDEPRESSANTS

A phase III randomised, double-blind, placebo-controlled, crossover trial of nortriptyline in participants with CisPN showed no benefit on paraesthesia or neuropathic symptoms, although there was an improvement in sleep ( $p < 0.02$ ) [284]. Amitriptyline has shown no efficacy for the improvement or prevention of CIPN symptoms in two double-blind, randomised, placebo-controlled trials [285, 286].

## SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI)

There is limited evidence for the use of SSRIs in painful CIPN [232].

## SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITOR (SNRI)

Studies in experimental models of painful neuropathy have demonstrated a superior antinociceptive effect of norepinephrine compared to serotonin [287], and combined increases in both serotonin and norepinephrine result in a better analgesic effect than an increase in either one alone [288]. A multicentre

randomised, double-blind, placebo-controlled crossover trial demonstrated the efficacy of duloxetine in participants undergoing platinum or taxane chemotherapy regimens [289]. At 5 weeks, participants receiving duloxetine reported a greater mean decrease in pain score compared to placebo (1.06 [95% CI 0.72–1.40] vs 0.34 [95% CI 0.01–0.66]  $p = 0.003$ ) [290]. Similar results have been reported in other smaller studies [291, 292]. Further, participants with painful OIPN are more likely to respond to duloxetine than those with TIPN [293]. Duloxetine has a greater effect than venlafaxine on pain scores [294]. Recent ASCO guidelines advise a moderate recommendation for the use of duloxetine in CIPN [232]. A randomised, double-blind, placebo-controlled phase III trial found greater improvements in pain relief by  $\geq 50\%$  in participants receiving venlafaxine compared to placebo ( $p = 0.02$ ) [295]. A retrospective cohort study of participants with painful TIPN or OIPN found that venlafaxine achieved relief of paraesthesia in over half the participants for up to 9 weeks ( $p < 0.001$ ) [296]. However, a small pilot randomised, placebo-controlled, double-blind study found no significant effect of venlafaxine in the prevention of OIPN [297].

## CONCLUSION

CIPN is a major dose-limiting side effect of chemotherapy, and the burden of CIPN continues to increase with increasing cancer-survivorship. Clinical guidance for the treatment of CIPN highlights the paucity of preventative strategies and symptom management. The diagnosis and assessment of CIPN lacks a reference standard, with studies utilising heterogeneous CIPN assessment tools dependent on self-reported outcome measures. The recent ACTION recommendations endorse a pathomechanism-driven treatment discovery approach to CIPN. CCM may provide an adjunct to NCS in natural history studies and trials of disease-modifying therapies. Detailed mechanistic research in CIPN and CIPN-related neuropathic pain is needed to address the substantial burden on the patient, families and society.

## ACKNOWLEDGEMENTS

**Funding.** Jamie Burgess gratefully acknowledges the support given by the Pain Relief Foundation in the form of a PhD studentship whilst writing this manuscript. No funding or sponsorship was received for the publication of this article.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Authorship contributions.** All persons who meet authorship criteria are listed as authors. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Conceptualisation, Uazman Alam and Jamie Burgess; writing—original draft preparation, Jamie Burgess, Maryam Ferdousi, Anne Marshall and Uazman Alam; writing—review and editing, Jamie Burgess, Kohei Matsumoto, David Gosal, C.B., Andrew Marshall, Tony Mak, Anne Marshall, Bernhard Frank, Rayaz A Malik, Uazman Alam; visualisation, Jamie Burgess and Uazman Alam; supervision, Uazman Alam. All authors have read and agreed to the published version of the manuscript. All included figures were created with Biorender.com.

**Disclosures.** Jamie Burgess, Uazman Alam, Maryam Ferdousi, David Gosal, Anne Marshall, Tony Mak, Andrew Marshall, Bernhard Frank, Rayaz A Malik and Uazman Alam have nothing to disclose. Cheng Boon's affiliation changed during the manuscript's production from the Department of Clinical Oncology, The Clatterbridge Cancer Centre, Wirral, UK to the Department of Clinical Oncology, The Royal Wolverhampton NHS Trust, Wolverhampton, UK.

**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

**Data availability.** Data sharing is not applicable for this article, as no datasets were generated or analyzed during the current study.

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