Chemotherapy-Induced Peripheral Neuropathy: Assessment, Phenotypes and Risk Factors

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**Statement of originality**

This is to certify that to the best of my knowledge; the content of this thesis is my own work.

This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Signature:

Name: Hannah Charlotte Timmins

Date: 26th February 2021

The chapters presented in this thesis resulted from research undertaken at the University of Sydney.

**Publications**

The following publications are a result of this thesis. In addition to parts of the Literature review (chapter 1), chapters 3, 4, 5, 6 and 7 of this thesis are published as below in which I designed the study, collected and analysed the data and wrote the drafts of the manuscripts.

**Literature Review**


Chapter 3

Chapter 3 of this thesis is published as:

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patients: a systematic review. J Cancer Surviv. 2021 Jan 12. doi: 10.1007/s11764-021-00988-x. Epub ahead of print. PMID: 33438175. I designed the study, analysed the data and wrote the drafts of the MS.

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Chapter 7 of this thesis is published as:

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In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

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As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

**Signature:**

**Supervisor name:** A/Prof. Susanna B. Park

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Abstract

This thesis examined treatment specific chemotherapy-induced peripheral neuropathy (CIPN) profiles and explored patient characteristics which may contribute to CIPN severity utilising multimodal CIPN assessment in taxane and oxaliplatin treated patients.

Initially, bilateral neuropathy assessments including clinical examination, neurophysiology and patient questionnaires revealed discrepancies between the patient experience and objective CIPN following taxane treatment. Further electrophysiological assessments revealed features more typical of entrapment neuropathy present in >50% of taxane-treated patients. These studies provided evidence for the variability in the clinical presentation of CIPN, highlighting discrepancies between the clinical definition, objective assessment, and patient experience and emphasising the need for a multimodal approach.

Studies were undertaken in in a homogenously treated cohort of paclitaxel treated patients to elucidate the phenotypic profile and longitudinal development of CIPN and assess the role of dose modification on neuropathy outcomes. Neuropathy was evident early in the treatment course and demonstrated limited recovery, identifying CIPN as a persistent neurological sequela. When evaluating the role of dose modification, patients who received dose reduction had worse patient and clinical neuropathy outcomes compared to those who received the full dose three months post-treatment, suggesting that individual risk factors likely play an important role in addition to cumulative dose.

A systematic review of the literature surrounding metabolic risk factors and their association with CIPN was undertaken and identified potential patient characteristics which are prevalent in the general population, including obesity and metabolic dysfunction.

Finally, the role of obesity on symptomatic, objective, and functional CIPN outcome measures was investigated, with overweight cancer survivors demonstrating significantly worse CIPN across symptomatic, objective clinical and functional outcomes compared to those with a
normal body mass index (BMI). This study also identified older age, larger waist circumference and larger body surface area (BSA) as predictors of CIPN severity.

In summary, this thesis has demonstrated variability in clinical presentation of taxane-induced neuropathy, provided a comprehensive understanding of the clinical manifestations and outcomes of weekly paclitaxel-induced neuropathy, highlighted the variation in response to dose modification on neuropathy outcomes and identified potential risk factors which are prevalent in the general population. The findings established in this thesis will assist in the development of appropriate assessment tools allowing for the identification of early CIPN and neuroprotective strategies. Additionally, understanding CIPN risk profiles and treatment specific neuropathy phenotypes will also assist with treatment decisions, and identification of patients who require intervention and supportive care, enabling personalised medicine and subsequently improving clinical outcomes for cancer survivors.
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ABBREVIATIONS

ANS Autonomic nervous system
BMI Body mass index
BSA Body surface area
CCM Corneal confocal microscopy
CIPN Chemotherapy-induced peripheral neuropathy
CMAP Compound muscle action potential
CNS Central nervous system
CSAP Compound sensory action potential
CT Computed tomography
CTS Carpal tunnel syndrome
CV Conduction velocity
DRG Dorsal root ganglion
DSP Distal symmetric polyneuropathy
EORTC-QLQ-CIPN20 European Organization for Research and Treatment of Cancer Quality of life CIPN20 Questionnaire
ECOG Eastern Cooperative Oncology Group
FACT/GOG-Ntx13 Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity
GWAS Genome wide association studies
FOLFOX 6 Oxaliplatin containing treatment regimen with 85 mg/m². oxaliplatin combined with leucovorin and 5-fluorouracil (5-FU)
IENFD Intraepidermal nerve fibre density
IQR Interquartile range
LFN Large fibre neuropathy
**LBM** Lean body mass

**LI** Laterality index

**LLN** Lower limit of normal

**NCI-CTCAE** National Cancer Institute Common Terminology Criteria for Adverse Events

**NCS** Nerve conduction studies

**NES** Nerve excitability studies

**P-APS** Paclitaxel-associated acute pain syndrome

**PN** Peripheral neuropathy

**PNS** peripheral nervous system

**PROM** Patient reported outcome measures

**QST** Quantitative sensory testing

**RDI** Relative dose intensity

**SEM** Standard error of the mean

**SFN** Small fibre neuropathy

**SNAP** Sensory nerve action potential

**SNPs** Single nucleotide polymorphisms

**SORT** Strength of Recommendation Taxonomy

**TNSc** Total Neuropathy Scale – clinical version

**TNSr** Total Neuropathy Scale – reduced version

**VF** Von Frey monofilaments
Chapter 1

Literature Review
INTRODUCTION

Long-term cancer survival rates (>5 years after diagnosis) are increasing globally, thanks to advancements in cancer diagnosis and treatment (Siegel et al. 2020). In Australia, greater than 68% of cancer patients will survive long-term (Australian Institute of Health and Welfare, 2019). As such, increased survival rates have created a new research focus, to improve long-term quality of life in cancer survivors. A key facet of this research agenda is in understanding potential side effects of cancer treatment. Over 50% of long-term survivors represent individuals who have been affected by breast, ovarian, lung, colorectal and haematological malignancies, which are commonly treated with neurotoxic chemotherapies (Jemal et al. 2019). These chemotherapies can produce peripheral nerve damage often resulting in long-term functional disability for cancer survivors. Patients treated with oxaliplatin and taxanes represent the largest cohorts of cancer survivors and are likely at-risk of experiencing long-term sequelae following cancer treatment (Jemal et al. 2019).

This literature review will present an overview of the clinical characteristics of peripheral neuropathy with specific relevance to oxaliplatin and taxane-induced peripheral neuropathy including, assessment strategies, key mechanisms, and risk factors.

OVERVIEW OF THE PERIPHERAL NERVOUS SYSTEM

The human nervous system consists of two major anatomical divisions, the central nervous system (CNS) consisting of the brain and spinal cord and the peripheral nervous system (PNS). The PNS is comprised of the remaining neural tissue and is responsible for relaying signals to and from the CNS via afferent and efferent pathways (Saladin 2010). The PNS is broadly divided into sensory (afferent) and motor (efferent) divisions with visceral and somatic subdivisions. The visceral motor division, also referred to as the autonomic nervous system
(ANS) operates outside of conscious control eliciting sympathetic or parasympathetic responses (Saladin 2010). The somatic nervous system includes cranial, spinal and peripheral nerves, in addition to some peripheral components of the autonomic nervous system (Dyck et al. 2005).

The communicative role of the nervous system is primarily carried out by neurons (Fig.1.1), which possess fundamental properties such as excitability, conductivity and secretion allowing for effective communication with other cells (Kiernan et al. 2013). Information via electrochemical stimulation is received from other neural cells and propagated via multiple branched protoplasmic extensions (dendrites) to the cell body (soma), which contains the nucleus and other organelles. The cell bodies of somatic motor neurons are housed within the ventral horn of the spinal cord. Conversely the somas of sensory nerve fibres are located outside the spinal cord in the dorsal root ganglion (Bear 2007). Impulses are carried away from the soma via a solitary axon to the terminal arborization which allows for the formation of synapses with other cells (King 2013).

Action potentials are produced by variations in sodium (Na\(^+\)) and potassium (K\(^+\)) conductance, with the sequence of changes in membrane potential being driven by alterations in ion flow across the cell membrane (Hille 2001; Barnett and Larkman 2007). Resting membrane potential is maintained by the electrical potential differences across the membrane generated by greater concentrations of Na\(^+\) outside the cell and higher concentrations of K\(^+\) inside. An influx of Na\(^+\) drives depolarisation to threshold, rapidly increasing the membrane potential from usually -70mV at rest, to +40mV (Hille 2001; Barnett and Larkman 2007). A complete action potential is produced once the threshold for excitation is reached, which subsequently travels down the axon depolarising adjacent areas via saltatory conduction (Hille 2001). The inactivation of Na\(^+\) channels initiate repolarisation towards resting membrane potential, with the activation of K\(^+\) channel serving to stabilise the membrane potential (Schwarz et al., 1995)
and contributing to hyperpolarisation, a consequence of repolarisation which overshoots the baseline resting membrane potential (Baker et al., 1987).

Axons may be sheathed in myelin, which is formed in the PNS by Schwann cells and acts to insulate the axon from extracellular fluid. The thickness of the myelin sheath in addition to the diameter and capacitive properties of the axon act to influence the speed of which impulses are conducted (King 2013). Myelinated axons demonstrate considerably faster conduction velocity than unmyelinated axons, via salutatory conduction. This is achieved through nodes of Ranvier, unmyelinated sections of axon which enable electrical impulses to ‘jump’ between nodes and facilitate impulse transmission (King 2013).

Figure 1.1 Basic components of a myelinated sensory neuron illustrating the cell body or soma located in the dorsal root ganglia, the axon and myelin sheath and unmyelinated nodes of Ranvier.
Large peripheral axons (Fig.1.2) classified as group A, are myelinated and thus represent the fastest conducting somatic afferent and efferent fibres (King 2013). The largest efferent neurons (Aα) innervate extrafusal muscle fibres, responsible for controlling effector skeletal muscle contraction and relaxation (Table 1.1). These alpha motor neurons can supply multiple skeletal muscle fibres, collectively forming the motor unit (Catala and Kubis, 2013). Aγ fibres are fusimotor neurons which adjust the sensitivity of the muscle spindle involved in deep tendon and muscle stretch reflexes, with Aβ neurons being both skeletomotor and fusimotor fibres (King 2013). Large afferent fibres are responsible for proprioception, pressure and vibration sensation (Lefaucheur et al. 2004). Sympathetic preganglionic efferent fibres, group B, and somatosensory Aδ fibres are slow conducting myelinated fibres. C fibres are unmyelinated and conduct nerve impulses slowly (De Andres et al. 2005). Though without a myelin sheath, multiple unmyelinated fibres are enveloped in a single Schwann cell to form the neurilemma, which has a protective and regenerative role (King 2013). Aδ-fibres are responsible for conveying cold and nociceptive input, while unmyelinated C-fibres convey innocuous warm and cold sensations, as well as noxious information from mechanical, thermal and chemical stimuli (Table 1.1). Both Aδ and C-fibres are involved in autonomic functioning by contributing to pre- and post-ganglionic fibres respectively, innervating structures including sweat glands, blood vessels and the heart (Themistocleous et al. 2014).
OVERVIEW OF PERIPHERAL NEUROPATHY

Damage to the peripheral nerves, known as peripheral neuropathy, results in interruption of information flow to and from the central nervous system. A variety of symptom presentations can occur depending on the location and mechanism of the damage. Similarly, the potential for regeneration and recovery from damage to a peripheral nerve fibre differs depending on the mechanism and extent of damage. In total, peripheral neuropathy contributes to functional impairment and health care costs due to its association with increased opioid use, falls risk, disability, and reduced life expectancy (Hoffman et al. 2015).
Peripheral neuropathy can be caused by many factors, including a range of metabolic, immune-mediated, and inherited conditions as well as exposure to exogenous substances. Around 1.6% of the population have peripheral neuropathy, with the incidence increasing to 6.6% for those over the age of 60 (Hoffman et al. 2015). The aetiology of peripheral neuropathy may not always be clear, with nearly half of all cases classified as idiopathic (De Greef et al. 2018, Khoshnoodi et al. 2016, Hoffman et al. 2015). Diabetes is the most common aetiology, estimated to account for 38% of polyneuropathy cases (Devigili et al. 2008). Entrapment mononeuropathies are also common in the generally population with the prevalence of the most common manifestation, carpal tunnel syndrome, estimated to be between 2.8% - 16% depending on age, gender, and other demographic factors (De Krom et al. 1992, Atroshi et al. 1999, Ferry et al. 1998).

**Clinical characteristics of peripheral neuropathy**

The clinical characteristics of peripheral neuropathy depend on the type of fibres damaged. Large fibre neuropathy (LFN, Table 1.1) typically results from damage to large myelinated (group A) somatic afferent and efferent fibres, resulting in motor and sensory disturbances (Table 1.2.). Damage to group A efferent fibres can result in symptoms including cramping, weakness and impairment of fine motor movement and reflexes, with greater peripheral damage associated with muscle atrophy and paralysis (Donofrio 2012). Testing of deep tendon reflexes also assesses muscle spindle receptors associated with $A\alpha$ (type I) afferent fibres. Reduced reflexes or loss of joint position sense can be indicative of damage to $A\alpha$ (type I) sensory fibres. Tactile or vibratory skin sensation is associated with mechanoreceptors to touch, pressure and vibration. Loss in these modalities is often indicative of $A\beta$ (Type II) sensory fibre dysfunction, with patients frequently describing numbness and paraesthesia (Lefaucheur et al. 2004).
Table 1.1 Nerve fibre type and function

<table>
<thead>
<tr>
<th>Fibre type</th>
<th>Function</th>
</tr>
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</table>
| Aα         | Proprioception  
Motor  
Spindle receptors- involved in reflexes  
| Aβ         | Touch, pressure and vibratory sensation  
Skeletomotor and fusimotor  
| Aγ         | Adjust the sensitivity of the muscle spindle- involved in deep tendon and muscle stretch reflexes  
| Aδ         | Cold, touch and nociceptive input  
Some autonomic functioning  
| B          | Sympathetic preganglionic efferent  
| C          | Innocuous warm and cold sensations  
Noxious information from mechanical, thermal, and chemical stimuli.  
Post ganglionic sympathetic fibres  

Small fibre neuropathy (SFN, Table 1.1) results from damage to Aδ (Type III)-fibres and C-fibres (Devigili et al. 2008, Karlsson et al. 2018, Themistocleous et al. 2014). SFN is typically associated with common sensory symptoms including burning, prickling, aching, electric shock, or itching sensations (Table 1.2.), although the severity and presentation of symptoms may vary (Terkelsen et al. 2017). Patients may also experience restless legs or foot movements and may report reduced or absent sensitivity to cold, heat, and noxious mechanical stimuli (Terkelsen et al. 2017). Symptoms of autonomic involvement associated with SFN may include postural hypotension, gastrointestinal or sexual dysfunction, dry eyes, dry mouth, variations in sweating and difficulty with urinary frequency and/or voiding (Table 1.2.) (Hovaguimian et al. 2011, Themistocleous et al. 2014).
Table 1.2. Examples of large and small fibre neuropathy symptoms

<table>
<thead>
<tr>
<th>Large fibre</th>
<th>Small fibre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Motor</td>
</tr>
<tr>
<td>Loss of joint position</td>
<td>Reduced reflexes</td>
</tr>
<tr>
<td>Reduced reflexes</td>
<td>Muscle cramping</td>
</tr>
<tr>
<td>Numbness and Paraesthesia</td>
<td>Altered gait</td>
</tr>
<tr>
<td>Impaired vibration</td>
<td>Weakness</td>
</tr>
<tr>
<td>sensation</td>
<td>cold, heat, and</td>
</tr>
<tr>
<td></td>
<td>noxious mechanical</td>
</tr>
<tr>
<td></td>
<td>stimuli</td>
</tr>
</tbody>
</table>

CHEMOTHERAPY-INDUCED NEUROPATHY

Chemotherapy-induced peripheral neuropathy (CIPN) is a major side effect of treatment with neurotoxic cancer treatments, including platinum compounds and taxanes. Symptoms of CIPN include paraesthesia, numbness, and weakness in the extremities, typically resulting from damage to large sensory and occasionally motor nerve fibres. However, small fibre components of the peripheral nervous system can also be affected, resulting in autonomic dysfunction and pain (Park et al. 2013). Long-term patient burden is common, with residual CIPN often present years after treatment cessation (Park et al. 2011b, Bandos et al. 2018) resulting in increased health care cost, poorer functioning and diminished quality of life (Mols et al. 2014, Pike et al. 2012, Winters-Stone et al. 2017).
Due to a dearth of neuroprotection and treatment, dose modification remains the only recommended strategy to mitigate neurotoxicity (Loprinzi et al. 2020). Subsequently, the tolerability of effective anti-cancer treatment may be reduced, impacting clinical and survival outcomes (Denduluri et al. 2018). As neurotoxic treatments are often used in cancers with increasingly high survival rates, a large number of cancer survivors are likely to experience CIPN as a long-term sequelae (Park et al. 2013, Pereira et al. 2016). However, the estimated occurrence of CIPN resulting from neurotoxic cancer treatments varies widely, reflecting the heterogeneity in CIPN definition, assessment method and time point, treatment regime and patient groups between studies (Pereira et al. 2016, Colvin 2019).

Despite the impact and prevalence of CIPN, there is limited understanding of the underlying pathophysiological mechanisms responsible for CIPN due to a paucity of standardised CIPN assessment and a lack of consensus on a ‘gold standard’ measurement and individual risk factors (Park et al. 2013, Knoerl et al. 2019). Moreover, the limitation of current tools and standard clinical approaches, which infrequently involve multimodal and comprehensive neurological assessment have resulted in the prevalence and phenotypic profiling of CIPN remaining poorly defined. (Cavaletti et al. 2010, Griffith et al. 2010, Park et al. 2013). As such, an improved understanding of CIPN assessment and phenotypic profiles would assist in contributing to personalised treatment and identification of neuroprotective strategies.

**MEASURING NEUROTOXICITY**

Quantification of CIPN remains a challenge, with a lack of consensus for the best clinical methods representing an ongoing limitation of this area of research (Griffith et al. 2010, Park et al. 2011b). Many of the current assessment tools often show a lack of concurrence with patient report and lack sensitivity to change (Forsyth et al. 1997). Consequently, gaps remain in identifying phenotypic profiles and underlying pathophysiological mechanisms and
providing accurate guidelines to clinicians. Despite a lack of consensus on diagnostic guidelines and assessment (Hoeijmakers et al. 2012), a range of tools have been developed to assist in measuring nerve function and quantifying damage in the clinical setting (Table 1.3).

**Clinician grading scales**

The most commonly used method to grade CIPN are clinician based-grading scales such as the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (U.S. Department of Health and Human Services, 2010). The NCI-CTCAE scale utilises a four-point grading scale to evaluate the extent and interference of CIPN (Table 1.4). The NCI-CTCAE is easy to administer, subsequently being a favoured choice for both the clinical setting and large-scale clinical trials (Salgado et al. 2020). However, despite being used extensively the NCI-CTCAE is limited by lack of validity, sensitivity, and limited responsiveness to change (Postma et al. 1998, Griffith et al. 2014, Cavaletti et al. 2013). Compared to other adverse events, CIPN is particularly vulnerable to the limitations of the NCI-CTCAE, due to a lack of objective thresholds and reliable grading of CIPN severity (Salgado et al. 2020). Though clinician training can improve reliability, there remains only a moderate level of inter-observer agreement (Cavaletti et al. 2013) and significant discrepancies with patient symptom reports (Cirillo et al. 2009, Bennett et al. 2012). The widespread use of the NCI-CTCAE is a limitation of the field of research due to its inadequacy as a reliable and sensitive CIPN assessment tool (Colvin 2019). Though the NCI-CTCAE retains some clinical utility (Frigeni et al. 2011), investigation into more reliable and valid assessment tools to facilitate CIPN monitoring and evaluations of neuroprotectants is required.
Patient reported outcome measures

Patient reports of symptoms are frequently used by clinicians to assess neuropathy; however, clinician interpretation of these symptoms can vary greatly. For instance, in a study of oxaliplatin-treated patients, 60% reported symptoms of neuropathy, with only 10% of these symptom reports being documented by clinicians (Bennett et al. 2012). Patient reported outcome measure (PROM) questionnaires have been developed to systematically survey symptoms and assess patient impact. Common to all self-reported measures, CIPN PROMs are subject to bias and measurement error (Cox-Martin et al. 2017). However, PROMs allow for patients to directly report their subjective experience of symptoms independent from clinician interpretation (U.S. Department of Health and Human Services 2006, Basch 2010).

Subsequently, PROMs are being increasingly utilised in both the clinical and trials settings to better quantify the patient experience of CIPN (Calvert et al. 2018, Basch et al. 2018).

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function</td>
<td>Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living</td>
<td>Sensory alteration of paresthesia interfering with activities of daily living</td>
<td>Disabling</td>
</tr>
</tbody>
</table>

Table 1.4. The National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4) (U.S. Department of Health and Human Services 2010). A clinician-based grading scale graded 0 (No CIPN) – 4 (CIPN is disabling).
Two of the most frequently used PROMs are the European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire-Chemotherapy Induced Peripheral Neuropathy (EORTC QLQ-CIPN20) scale (Postma et al. 2005a), and the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group Neurotoxicity (FACT/GOG-NTx) questionnaire (Calhoun et al. 2003) both of which utilise Likert scales to rate each item from 'not at' all to 'very much' in terms of symptom severity. The psychometric properties of these questionnaires have been extensively investigated (Calhoun et al. 2003, Lavoie Smith et al. 2013, Postma et al. 2005b, Cavaletti et al. 2013, Kieffer et al. 2017) with greater sensitivity and reliability for grading CIPN symptoms compared to the NCI-CTCAE (Lavoie Smith et al. 2013, Postma et al. 2005b).

In addition to these specific CIPN PROMs, general pain scales including the Neuropathic Pain Symptom Inventory, the Brief Pain Inventory, visual analogue rating scales and word descriptor lists to self-describe symptoms have also been used in patients with CIPN. However, these scales are non-specific and confounded by other types of neurological symptoms including myalgia and cancer pain, which can share overlapping pain and discomfort features (Attal et al. 2009, Delmotte et al. 2018a, Dougherty et al. 2007, Reddy et al. 2016, Boyette-Davis et al. 2011, Boyette-Davis et al. 2013, Delmotte et al. 2018b, Forstenpointner et al. 2018).

Though limited to patient perceptions of symptoms, and lacking insight into pathophysiological mechanisms, the inclusion of PROMs allows for an improved understanding of the impact of CIPN symptoms on the patient, and a better understanding of the relationship between patient experience and objective CIPN outcomes (Ezendam et al. 2014, Eckhoff et al. 2015).
Neurophysiological techniques

Nerve conduction studies

Conventional nerve conduction studies (NCS) are the gold standard for diagnosing large fibre neuropathy in the clinical neurological setting (Fuglsang-Frederiksen et al. 2011, Kandula et al. 2017). Information including compound action potential amplitudes, latency and conduction velocity can be acquired non-invasively, providing differentiation between axonal and demyelinating pathologies. NCS can confirm a diagnosis of CIPN, providing information reflecting the extent of axonal loss (Park et al. 2013). Reduction of compound sensory action potential (CSAP) amplitudes are a common finding following neurotoxic cancer treatment, suggesting the presence of a sensory predominant axonal polyneuropathy (Chaudhry et al. 1994, Lehky et al. 2004, Lomonaco et al. 1992, Argyriou et al. 2008). Moreover, NCS enable the differentiation of CIPN from other diagnoses, such as entrapment neuropathies which are localised to a particular nerve, whereas CIPN is a generalised neuropathy (Chen et al. 2013). However, despite providing some information on phenotypic neuropathy profiles and pathology, NCS are non-specific providing only limited insight into pathophysiological mechanisms (Kiernan et al. 2005). Moreover, NCS may lack sensitivity in the CIPN setting, with indication that NCS only identify dysfunction later in the treatment course (Postma et al. 2000, Park et al. 2009b). Further, NCS only provide information about large fibres and lack sensitivity to quantify action potentials from small fibres (Arezzo et al. 2002). Additionally, neurophysiological investigation of CIPN tends to only evaluate a limited number of nerves, with the sural nerve being commonly used as an index of CIPN (Griffith et al. 2014, Argyriou et al. 2019). However, the sural sensory nerve action potential (SNAP) represents responses from the large diameter Aβ sensory nerve fibres, which constitute only 30% of myelinated fibres in the sural nerve (Lefaucheur et al. 2004). Moreover, the sural nerve is a sensory nerve and does not contain motor afferents. Despite these limitations, NCS remain a standard in neurological assessment providing a means of objectively evaluating neuropathy. Specifically,
NCS have been shown to reliably identify patients at risk of developing severe neurotoxicity in chemotherapy-treated populations (Argyriou et al. 2005b, Velasco et al. 2014), suggesting NCS may be useful as an objective outcome in clinical trials for evaluating neuroprotective agents.

**Nerve excitability studies**

Nerve excitability studies (NES) are a non-invasive method of determining *in vivo* membrane potential and ion channel function (Kiernan et al. 2000, Kiernan et al. 2020). The majority of NES studies have evaluated the median nerve, which is a mixed motor/sensory nerve.

Similar to NCS, only large fibres can be assessed with NES. Moreover, lower limb NES can be challenging, with most recordings limited to the upper limbs (Park et al. 2013, Kiernan et al. 2020). However, persistent changes in the biophysical properties of nerves have been found in populations of cancer survivors (Park et al. 2009a, Park et al. 2009b, Park et al. 2011a, Kandula et al. 2020). Excitability changes specific to the type of chemotherapeutic agent have also been reported, suggesting greater resolution compared to traditional NCS (Kandula et al. 2020). Moreover, excitability changes have indicated the onset of oxaliplatin-induced neurotoxicity prior to changes in NCS and clinically significant symptoms, suggesting greater sensitivity to change and utility as a potential biomarker for identifying at risk patients (Park et al. 2013, Park et al. 2009b). Consequently, NES may help provide comprehensive neurophysiological neuropathy profiles and identify early signs of nerve damage in chemotherapy patients.

**Quantitative sensory testing**

Quantitative sensory testing (QST) is a non-invasive psychophysical assessment of thermal, mechanical and vibration sensation presented in a quantitative manner, allowing for the
assessment of different fibre types associated with these modalities. Unlike electrophysiological testing, which can only detect a loss of function; QST can also detect gain of function, broadening its utility for assessing the functionality of the entire somatosensory system (Backonja et al. 2013). However, it can be difficult to establish where along the sensory pathway dysfunction is occurring, due to poor spatial resolution (Shy et al. 2003). Though the sensory stimuli utilised are objective, the participant’s response is subjective and can vary based on the type of method used. Participants may be asked to indicate when an increasing stimulus is detected or decreasing stimulus is no longer detected known as the ‘limits’ method. This however can be subject to errors due to the participant’s reaction time (Shy et al. 2003). The method known as ‘forced choice’ or ‘levels’ in which the participant signals detection of stimuli presented at different intensity levels, is less affected by reaction time, but generally takes longer to implement (Shy et al. 2003). This variability along with difference in the instruments, training of the examiner and participant, location of testing and skin temperature can make QST unreliable for diagnosing individuals when used in isolation (Cazzato et al. 2017, Themistocleous et al. 2014). However, increasing consensus amongst special interest groups and the standardisation of rigorous protocols for QST examination (Rolke et al. 2006b) has assisted in developing the technique for clinical implementation and for use in clinical trials (Rolke et al. 2006a), with QST been utilised in CIPN as an outcome measure and to determine chemotherapy-specific neuropathy profiles (Argyriou et al. 2019). CIPN is typically associated with large fibre impairments indicated by touch and vibration thresholds, however different patterns of impairments in modalities relating to chronic dysfunction in Aβ, Aδ- and C-fibres have been demonstrated in patients treated with taxanes and platinum compounds (Forsyth et al. 1997, Attal et al. 2009, Binder et al. 2007, Boyette-Davis et al. 2013, Chaudhry et al. 1994, De Carvalho Barbosa et al. 2014, Delmotte et al. 2018a, Hershman et al. 2011, Kokotis et al. 2016, Krøigård et al. 2014, Nahman-Averbuch et al. 2011, Reddy et al. 2016). Though this variation in QST findings between chemotherapy
types may reflect differences in methodology, these different patterns of impairments in
modalities may potentially elucidate differences in pathophysiological mechanisms.

**Total neuropathy score**

The Total Neuropathy score (TNS; Johns Hopkins University) (Cornblath et al. 1999) is a
composite grading measure of symptom report, clinical examination and neurophysiological
parameters. Though limited to the assessment of large nerve fibres, the TNS has been
validated in a multicentre setting as a sensitive measure of CIPN (Cavaletti et al. 2006) and
addresses some of the limitations of the NCI-CTCAE. The larger range of scoring values (0-28)
allows for more precise grading and greater responsiveness to change. Subsequently the TNS
is less prone to ceiling and floor effects compared to the NCI-CTCAE and addresses the lack
of distinction between moderate and severe neurotoxicity (Frigeni et al. 2011). However,
changes in the score are nonspecific to the type of chemotherapeutic agent and do not
provide specific mechanistic information.

Multiple iterations of the TNS exist, all of which have been validated in patients with CIPN and
demonstrate good interrater reliability (Smith et al. 2010, Cavaletti et al. 2007). In routine
clinical practice, use of the clinical version (TNSc) which omits NCS, may be more appropriate
as it does not require specialised equipment or training. However, the addition of objective
neurophysiological measures may increase the objectivity of the scale increasing its utility as a
primary outcome measure in clinical trials of neuroprotective agents (Cavaletti et al. 2010,
Argyriou et al. 2019).

**Skin biopsy**

Skin biopsy allows for quantification of intraepidermal nerve fibre density (IENFD), reflecting
small nerve fibre density. Current recommendations for conducting skin biopsy suggest taking
a 3-mm punch skin biopsy at the distal leg 10 cm above the lateral malleolus, though biopsies from the proximal thigh may provide additional information (Lauria et al. 2010). Comparison with normative reference values is required for a diagnosis however, as the IENF density can decline with age and vary between males and females, normative values must be adjusted accordingly (Lauria et al. 2010). Despite requiring some technical expertise (Ferrari et al. 2013), skin biopsy is minimally invasive and shows good concurrence with clinical findings and neuropathy scales across multiple disorders including diabetes, HIV and idiopathic neuropathy (Truini et al. 2014, Callaghan et al. 2020a, Lauria et al. 2010).

Reduction in IENFD has been demonstrated in skin biopsies from oxaliplatin and docetaxel treated patients (Krøigård et al. 2014, Burakgazi et al. 2011). However, these findings have been inconsistent with other studies finding no, or even increased IENFD following neurotoxic treatment (Velasco et al. 2017, Koskinen et al. 2011, Bechakra et al. 2018).

**Corneal Confocal Microscopy**

Corneal Confocal Microscopy (CCM) allows for non-invasive in vivo quantification of small nerve fibres in the cornea (Hoeijmakers et al. 2012). Multiple scans are collected to capture the entire depth of the cornea and quantify indicators of corneal nerve fibre damage (Tavakoli et al. 2011). Manual or automatic assessment of the number of major nerves/mm² of corneal tissue (Corneal nerve fibre density); the number of branches emanating from major nerve trunks/mm² of corneal tissue (corneal nerve branch density); the total length of all nerve fibres and branches (corneal nerve fibre length), and corneal nerve fibre tortuosity serve as established indicators of damage and/or repair (Malik et al. 2003, Quattrini et al. 2007).

CCM has been verified in multiple forms of neuropathy including diabetic, immune-mediated, and idiopathic (Tavakoli et al. 2011, Lalive et al. 2009, Tavakoli et al. 2010). CCM demonstrates good correlation with IENFD (Chen et al. 2015) and recent improvements in
technique, analysis of corneal nerve images and the availability of normative values (Cazzato et al. 2017) suggest that CCM may be a reliable biomarker of neuropathy (Quattrini et al. 2007).

There has been limited use of this novel method in chemotherapy treated cohorts. Studies utilising CCM in oxaliplatin and docetaxel treated patients failed to show evidence of deficits during treatment, with measures of CCM showing no change (Campagnolo et al. 2013, Ferdousi et al. 2015, Bennedsgaard et al. 2020, Chiang et al. 2021). However, these studies should be interpreted with caution due to their small sample size and lack of replication in chemotherapy-treated cohorts.

**CIPN Assessment Tool Summary**

Currently there is a lack of agreement on optimal primary outcome measures in assessing CIPN which has implications for both clinical trials and epidemiological studies assessing risk factors (Sucheston-Campbell et al. 2018). The advantages and disadvantages of these assessment tools are presented in Table 1.3. A substantial amount of the variability in neuropathy incidence can be attributed to the use of different outcome measures in different studies and settings. However, there is increasingly consensus that a multimodal approach combining subjective patient-reported outcomes with objective assessments may provide the most optimal strategy for evaluating CIPN (Argyriou et al. 2019).
<table>
<thead>
<tr>
<th>Assessment tool</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinician grading scale: NCI-CTCAE</strong></td>
<td>A four-point grading scale to evaluate the extent and interference of CIPN based on clinician impression</td>
<td>Easy and quick to administer</td>
<td>Lack of validity, sensitivity, and limited responsiveness to change</td>
</tr>
<tr>
<td><strong>Patient reported outcome measures</strong></td>
<td>Questionnaires which systematically survey symptoms and assess patient impact</td>
<td>Allows for patients to directly report symptoms independent from clinician interpretation</td>
<td>Subject to bias and measurement error</td>
</tr>
<tr>
<td><strong>Nerve conduction studies</strong></td>
<td>Gold standard neuropsychological technique for diagnosing large fibre neuropathy in the clinical neurological setting</td>
<td>May reliably identifying patients at risk of severe neurotoxicity</td>
<td>May lack some sensitivity in the CIPN setting</td>
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<td></td>
<td></td>
<td>Non-invasive, objective indicator of nerve dysfunction</td>
<td>Only evaluate a limited number of nerves</td>
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<td></td>
<td></td>
<td>Provides some differentiation between axonal and demyelinating pathologies</td>
<td>Non-specific providing only some insight into pathophysiological mechanism</td>
</tr>
<tr>
<td><strong>Nerve excitability studies</strong></td>
<td>Non-invasive, objective indicator of nerve dysfunction</td>
<td>Only assess large fibres</td>
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<tr>
<td>Neuropsychological technique for evaluating in vivo membrane potential and ion channel function</td>
<td>Excitability changes specific to the type of chemotherapeutic agent have been reported, suggesting greater resolution compared to traditional NCS</td>
<td>Lower limb NES can be challenging, with most recordings limited to the upper limbs</td>
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<td></td>
<td>Greater sensitivity to change than NCS</td>
<td>Requires expertise and specialist equipment</td>
<td></td>
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<tr>
<td></td>
<td>Identify early, pre-symptomatic signs of nerve damage</td>
<td>Novel technique</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>Quantitative sensory testing</strong></th>
<th>Non-invasive psychophysical assessment of thermal, mechanical and vibration sensation</th>
<th>Able to detect both loss and gain of function</th>
<th>Poor spatial resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quantitative clinical assessment of different modalities</td>
<td>'Limits' method subject to errors due to reaction time</td>
<td>Participant's responses are variable between methods</td>
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<tr>
<td></td>
<td>Allows for assessment of different nerve fibre types</td>
<td>Time consuming</td>
<td></td>
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<td></td>
<td>Consensus guidelines available for clinical and research implementation</td>
<td>Widely used as a research tool in CIPN</td>
<td>Differences in instruments, training, test location and skin temperature can lead to variability</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Non-invasive, cost effective and easy to implement</td>
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<td></td>
<td></td>
<td></td>
<td>Lacks reliability for diagnosing individuals when used in isolation</td>
</tr>
<tr>
<td><strong>Skin biopsy</strong></td>
<td>Quantification of intraepidermal nerve fibre density and innervated skin structures</td>
<td>Quantification of IENFD and innervated skin structures as a marker of SFN</td>
<td>IENFD affected by age and gender</td>
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<td></td>
<td>Good concurrence with clinical findings and neuropathy scales across multiple disorders</td>
<td>Displays stability over time</td>
<td>Requires some technical expertise</td>
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<td></td>
<td>Sensitivity to change even in the presence of normal NCS results</td>
<td></td>
<td>Minimally invasive</td>
</tr>
<tr>
<td><strong>Composite grading measure: Total neuropathy score</strong></td>
<td>Multimodal composite grading measure incorporating symptom report, clinical examination and NCS</td>
<td>More precise grading and greater responsiveness to change</td>
<td>Changes in scores not specific to chemotherapeutic agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple versions which have been validated</td>
<td>Extended versions require specialist equipment and training</td>
</tr>
<tr>
<td><strong>Corneal Confocal Microscopy</strong></td>
<td>Non-invasive in vivo quantification of small nerve fibres in the cornea</td>
<td>Non-invasive</td>
<td>Less established technique</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verified in multiple forms of neuropathy as a marker of SFN</td>
<td>Lack of replication in chemotherapy-treated cohorts</td>
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<tr>
<td></td>
<td></td>
<td>Demonstrates good correlation with IENFD</td>
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CLINICAL CHARACTERISTICS OF CIPN: OXALIPLATIN AND TAXANES

Oxaliplatin

Oxaliplatin is a 3rd generation platinum compound with proven efficacy in both early and advanced stage colorectal cancer (André et al. 2004). Oxaliplatin-induced neuropathy is the most prominent toxicity during and after treatment completion, representing a major cause of dose modification (Land et al. 2007, Velasco et al. 2014). A unique pattern of oxaliplatin-induced neurotoxicity has been well described, consisting of acute and chronic profiles (Lehky et al. 2004, Park et al. 2009a, Krishnan et al. 2005). Acute neurotoxicity follows infusion and leads to symptoms such as cold and mechanical allodynia for more than 90% of patients, however these symptoms generally resolve within a week (Kokotis et al. 2016, Park et al. 2009a). It has been reported that between 50-70 % of patients describe these cold-related symptoms as painful, with characteristics consistent with neuropathic pain (Delmotte et al. 2018b, Forstenpointner et al. 2018). However, others convey unpleasant but non-painful sensations, including paraesthesia which is generally attributed to large sensory fibre involvement (Ochoa et al. 1980). These findings are also in agreement with suggestions that oxaliplatin interferes with axonal ion conductance in Aβ-fibres, leading to sodium channel mediated hyperexcitability (Sittl et al. 2012). Evidence from human axonal excitability studies in large fibres also suggests that alterations in measures relating to sodium-channel function following oxaliplatin infusion may be responsible for the acute symptom profile (Park et al. 2009a, Heide et al. 2018). These acute changes appear more pronounced early in the treatment course and are mechanistically linked to the development of chronic neurotoxicity suggesting a large fibre aetiology (Park et al. 2009a). However, the association of different fibre types in the aetiology of these acute symptoms remains to be fully defined.
Cumulative doses of oxaliplatin exceeding 750 mg/m² lead to a chronic sensory neuropathy. However, ‘Costing’ is common following cessation of oxaliplatin, where neuropathy symptoms continue to progress, peaking in severity around three-months post completion (Pachman et al. 2015). Typical characteristics include distal paraesthesia and numbness (Gramont et al. 2000, Krishnan et al. 2005), suggestive of a predominately sensory large fibre dysfunction which can be confirmed by NCS (Kokotis et al. 2016, Krøigård et al. 2014) and abnormalities in QST modalities relating to large fibre function (mechanical and vibration detection thresholds) (Kokotis et al. 2016, De Carvalho Barbosa et al. 2014, Attal et al. 2009).

Chronic small fibre dysfunction is less well defined. Distal pain, predominately in the feet has been reported to persist in 25% of patients up to 20 months post oxaliplatin treatment, suggestive of long-term small fibre dysfunction (Ventzel et al. 2018). However, due to a lack of consistency in the use of neuropathic pain measures, as well as variations in time since completion, cumulative dose and the use of pain medication, estimates of neuropathic pain remain broad. Studies have reported the prevalence of neuropathic pain to ranging from 5% - 30% for oxaliplatin-treated patients (Wang et al. 2016, Ventzel et al. 2018, Velasco et al. 2017, Krøigård et al. 2014, De Carvalho Barbosa et al. 2014).

There is limited evidence for autonomic neuropathy associated with oxaliplatin treatment. However, oxaliplatin-related urinary retention, potentially a manifestation of autonomic dysfunction, has been reported in a case series of patients treated with a cumulative dose >1000mg/m² (Taieb et al. 2002). Prospective studies measuring alterations in cardiac rhythm and blood pressure in response to changes in posture, have revealed evidence of orthostatic hypotension and dysfunction in parasympathetic heart innervation six months post oxaliplatin treatment (Dermitzakis et al. 2014). However, these effects may not be exclusively attributable to oxaliplatin, as patients were receiving combination chemotherapy including 5-
fluorouracil/leucovorin which has been shown to produce its own profile of cardiotoxicity (Saif et al. 2009).

Taxanes

Taxanes including paclitaxel and its derivatives, docetaxel and abraxane are used in the treatment of a wide variety of malignancies including breast, prostate, ovarian, pancreatic and non-small cell lung cancer (Chen et al. 2013). A predominately sensory neuropathy can develop with cumulative doses exceeding 250mg/m² (Forsyth et al. 1997), with symptoms such as paraesthesia, dysesthesia and numbness in the extremities affecting up to 80% of patients treated with paclitaxel (Hershman et al. 2011, De luliis et al. 2015).

Neuropathic pain is less frequent, but of those affected by paclitaxel-induced peripheral neuropathy, 25-30% reported neuropathic pain in the hands and feet (Hershman et al. 2011, Sparano et al. 2008, Reyes-Gibby et al. 2009). Similarly reports of neuropathic pain in addition to large fibre symptoms of numbness and tingling have been reported to persist in docetaxel treated patients more than two years post completion (Krøigård et al. 2014). Additionally, a paclitaxel-associated acute pain syndrome (P-APS) has been described, with severity peaking at three-days post paclitaxel infusion (Loprinzi et al. 2011). Despite patients describing a predominately dull/aching pain mostly in the legs and feet, further investigation has revealed patient reports of shooting and burning pain, leading to the suggestion that P-APS may result from nociceptive neuron pathology (Loprinzi et al. 2011).

While autonomic dysfunction associated with taxanes is uncommon, paralytic ileus and orthostatic hypotension are the most likely autonomic disorders to occur following paclitaxel treatment, with diabetic patients potentially having more susceptibility (Tonkin 2009). Acute orthostatic hypotension and heart rate variation following paclitaxel infusion can be evident
even early in the course of treatment (Ekholm et al. 2000) and orthostatic hypotension has been observed three months post paclitaxel completion at cumulative doses >1700mg (Dermitzakis et al. 2016). Orthostatic hypotension is generally mild; however rare cases of severe orthostatic hypotension have been reported, with the aetiology being attributed to paclitaxel-induced sympathetic and parasympathetic autonomic neuropathy (Jerian et al. 1993).

**Recovery Profile**

CIPN associated with oxaliplatin was initially reported by early clinical trials to be reversible in most patients (André et al. 2004). However, over time a substantial body of work has disputed the reversibility of oxaliplatin-induced CIPN, with evidence suggesting deficits can persist long term (Pachman et al. 2015, Bennedsgaard et al. 2020, Selvy et al. 2020). Chronic CIPN was present in 64% of patients at one year (Ventzel et al. 2016), with little improvement reported between one- and five-years post completion in another study (31% vs 26% of symptomatic patients) (Selvy et al. 2020). While neuropathy symptoms often occur in both the hands and feet during treatment, lower limb neuropathy symptoms are most commonly reported to persist long-term (Pachman et al. 2015). A prospective study with objective neurophysiological outcome measures demonstrated persistence of chronic CIPN in 84% of oxaliplatin treated patients at two years (Briani et al. 2014). Neurophysiological recovery is often incomplete, with reductions in sensory amplitudes, consistent with sustained axonal neuropathy being reported up to five years post oxaliplatin completion (Kokotis et al. 2016, Padman et al. 2015, Pietrangeli et al. 2006). Similarly, persistent abnormalities in axonal excitability parameters suggestive of long-term alterations in axonal excitability have also been documented (Park et al. 2011b, Park et al. 2009b). Though the proportion of long-term symptomatic patients differs between studies, persistent neuropathy following oxaliplatin treatment is a consistent finding in many studies.
Similarly, reports of residual deficits from taxane-induced neuropathy are varied. In a prospective study, 34% of patients were still reporting clinically significant neuropathy compared to baseline two years after taxane cessation (Hershman et al. 2018). In a large trial of breast cancer patients, 41% remained symptomatic two years after taxane treatment initiation, with 10% still reporting symptoms as severe (Bandos et al. 2018). In another trial, 41% of patients also had some level of neuropathy three years after initiating treatment with paclitaxel (Tanabe et al. 2013). In a cross-sectional study, 81% patients reported neuropathy symptoms in their hands and/or feet, with severe symptoms being reported by 27% of patients in the hands and 25% in the feet. Patient reported neuropathy also correlated with deficits in vibration sensibility (Hershman et al. 2011). Limited neurophysiological recovery is also common, with up to 56% of patients demonstrating some evidence of sensory axonal neuropathy up to 13 years after taxane treatment (Osmani et al. 2012). Based on electrodiagnostic criteria, sensory polyneuropathy ranging from mild to severe was found in 67% of patients 9-months after taxane treatment (Chen et al. 2013). Similarly, patients reporting more severe neurotoxicity up to 4 years post paclitaxel treatment, were also observed to have persistently reduced sural amplitudes suggestive of axonal sensory neuropathy (Park et al. 2011a).
KEY RISK FACTORS ASSOCIATED WITH CIPN

Variations in the severity and onset of CIPN are often observed in the clinical setting highlighting the potential role of individual risk factors in CIPN development. However, the lack of consistency in assessing CIPN has implications for accurate epidemiological studies limiting consensus on factors associated with CIPN vulnerability (Colvin 2019). Nevertheless, some key treatment and patient factors have been investigated across multiple studies and are described below, focusing on taxane and oxaliplatin-treated cohorts.

Treatment-related factors

Increased cumulative dose is a well-recognised risk factor for CIPN, with dose modification being the only recommended strategy to mitigate neuropathy severity (Loprinzi et al. 2020). Specifically, cumulative dose is particularly implicated in platinum-induced neuropathy, with doses >800 mg/m² of oxaliplatin being associated with chronic neuropathy development (Beijers et al. 2014, Beijers et al. 2015, Ventzel et al. 2016). Similarly, higher cumulative doses have been associated with worsening neuropathy across taxane treatment, with greater severity associated with doses ≥300 mg/m² (Pereira et al. 2016, Winer et al. 2004).

Variation in the regime of administration may also influence the rate of neurotoxicity, with lower rates of paclitaxel-induced neuropathy being associated with three-weekly compared to weekly-regimes (Sparano et al. 2008, Pace et al. 2007, Huang et al. 2012, Seidman et al. 2008). However, this has not been confirmed universally with other trials demonstrating worse neuropathy for patients receiving taxane-treatment every three-weeks (Budd et al. 2015, Mauri et al. 2010). Similarly, delays between doses may not benefit oxaliplatin-induced neuropathy (Cioroiu et al. 2017) with three weekly regimes being comparable to 2-weekly administration, though this may be only applicable for schedules containing lower single doses (Argyriou et al. 2012). However, longer oxaliplatin-free intervals may be beneficial, with
“stop-and-go” treatment strategies associated with lower rates of severe neurotoxicity (Park et al. 2017b, Adams et al. 2011). Nevertheless, recent trials evaluating the efficacy of a three-month administration of oxaliplatin demonstrated reduced frequency of severe (NCI grade 3/4) peripheral neuropathy and comparable survival to patients receiving six months despite both groups receiving a similar cumulative oxaliplatin dose (Iveson et al. 2018, Grothey et al. 2018).

Dose and chemotherapy type may be factors which are amenable to modification, with further studies warranted to understand how a more individualised approach to chemotherapy dosing might impact on cancer survival and toxicity profiles. However, despite the association with cumulative dose, variations in the presentation of neuropathy can still occur amongst homogenously treated patients, suggesting a role for patient-specific risk factors.

**Patient Characteristics**

Some demographic attributes, comorbidities and genetic factors have been proposed as contributing towards an increased risk for CIPN.

Despite being addressed in several studies, the effect of pre-existing conditions on the risk of developing CIPN is controversial (Velasco et al. 2010a). Most commonly, diabetes has been the subject of investigation with much discord in the literature. Consequently, a systematic review of the literature evaluating diabetes and other metabolic risk factors for CIPN is addressed in chapter 6 of this thesis. Other clinical risk factors including pre-existing neuropathy, anemia, nutritional status, and supplement use have also been implicated in neuropathy risk from taxane and platinum treatment, however studies of these factors are limited (Robertson et al. 2018, Velasco et al. 2014, Greenlee et al. 2017, Rowinsky et al. 1993).
Advancing age is generally associated with morphological and functional changes in the PNS, with some level of degeneration occurring (Verdú et al. 2000). However, the role of age as a CIPN risk factor has been controversial. Older age had been associated with taxane-induced neuropathy, with older patients experiencing increased frequency and severity of clinically-graded CIPN (Lichtman et al. 2012). Similarly, CIPN risk was found to increase with age by 4% each year in another trial of taxane treated patients (Hershman et al. 2016). However, this cohort focused on patients over 65-years-old and therefore may be less representative of some clinical population of cancer survivors (Hershman et al. 2016). Based on patient symptom report, women over the age of 60 had an increased risk of experiencing long term CIPN, with older patients reporting significantly worse symptoms two years post taxane completion (Hershman et al. 2018). Older patients were also more likely to be reporting symptoms two-years post completion of taxanes in a prospective study (Greenlee et al. 2017). Similarly, age was found to be the only consistent risk factors for both clinician graded, and patient reported CIPN, despite generally poor agreement between the two measures (Park et al. 2017a).

However, in another large clinical trial of taxane treated patients, age was not associated with clinician graded neuropathy (Schneider et al. 2012). Similarly, age was not an independent risk factor for paclitaxel induced neuropathy, despite being a common adverse event (Barginear et al. 2019). In a small prospective study, no difference in CIPN severity was observed for paclitaxel-treated patients over the age of 65 based on clinical examinations and neurophysiological assessments (Argyriou et al. 2006).

For oxaliplatin treated patients, younger age (<60 years) has been reported to predict of longer neuropathy duration (Vincenzi et al. 2013), with advancing age being associated with a reduced risk of acute oxaliplatin-induced peripheral neuropathy (Alejandro et al. 2013). However, other studies have failed to find any association between age and neuropathy risk (Baek et al. 2010, Attal et al. 2009, Sugihara et al. 2012, Velasco et al. 2014).
The role of sex in CIPN development is unclear. Greater severity of CIPN on clinical examination has been reported for male patients following oxaliplatin based treatment (Velasco et al. 2014). However, conversely, female patients have also been described as reporting greater symptom severity following oxaliplatin treatment (Wiela-Hajeńska et al. 2015), although further investigations found no increased risk among women (Sugihara et al. 2012, Attal et al. 2009). In another study of patients receiving oxaliplatin treatment, the risk of clinically documented neuropathy was found to be comparable between males and females (Alejandro et al. 2013). Many studies investigating taxane induced peripheral neuropathy have centred around cohorts of female breast cancer survivors. Consequently, the role of sex is not readily examined in these cohorts and comparisons across trials provide limited insight (Kudlowitz et al. 2013). However, neurotoxicity based on the NCI-CTCAE has been reported to occur more frequently in females than males following paclitaxel treatment, in an analysis of multiple cancer types (De Graan et al. 2013).

Increasingly, the role of genetic polymorphisms in determining an individual’s treatment response and toxicity development have become a focus for understanding CIPN risk. A number of investigations utilising Genome wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) potentially associated with CIPN vulnerability. Specifically, genes involved in suspected key pathophysiological mechanisms have been identified. For taxanes, this includes SNPs in genes involved with microtubule dynamics and stabilisation (Park et al. 2014, Chua et al. 2020) and genes associated with mitochondrial dysfunction (Kober et al. 2018). Similarly, in line with clinical evidence, genetic variants associated with voltage-gated sodium channel function have been indicated as contributing to the pathophysiology of oxaliplatin-induced neuropathy (Palugulla et al. 2017, Sereno et al. 2017). Many other genes have been indicated in the development of CIPN such as those involved in axon outgrowth, drug metabolism, neuronal apoptosis and diabetic neuropathy (Sucheston-Campbell et al. 2018, Inada et al. 2010, Lam et al. 2016, Hertz et al.
However, though multiple polymorphisms have been identified, most have failed to be validated in further studies, with few holding across meta-analyses (Peng et al. 2013, Argyriou et al. 2020). The contribution of genetic factors to CIPN vulnerability is complex, likely involving multiple genes rather than being dependent on a single polymorphism (Cavaletti et al. 2011). Moreover, other patient characteristics may interact with genetic variants to increase CIPN risk (De Graan et al. 2013).

Some potential confounders affecting studies investigating risk factors include differing definitions and assessment of CIPN; varying dosing regimens and assessment time points (Colvin 2019). Moreover, most risk factors have been identified not from trials specifically designed to investigate CIPN risk factors, but from secondary analyses typically based on unimodal CIPN assessment tools. Studies specifically examining risk factors are often limited by small sample sizes (Flatters et al. 2017). Consequently, there is a lack of clear evidence regarding risk factors for CIPN obtained from randomised clinical trials and much heterogeneity in the findings of these studies, a common limitation of this field of research.

Identifying risk factors for the development and severity of CIPN is valuable for informing treatment decisions and mediating CIPN burden. However, the implementation of sensitive outcome measures in large scale clinical trials are required to further elucidate the patient-specific and treatment-related determinants of CIPN risk and to make progress in understanding the contribution of specific risk factors.
KEY MECHANISMS OF CIPN

Though similarities exist in the clinical presentation of CIPN induced by different chemotherapy types, variation in the specific phenotypes suggest differences in the underlying mechanisms. Further, CIPN pathology is likely to be multifactorial, limiting understanding and complicating advances in the development of neuroprotective strategies (Park et al. 2013, Zajączkowska et al. 2019). Further elucidating pathophysiological processes, including shared mechanisms between treatments may help to identify effective neuroprotective strategies and inform clinical decisions. While the underlying mechanisms of CIPN remain complex, the below section presents some of the key mechanisms identified as contributing to CIPN development associated with oxaliplatin and taxane treatment.

Damage to the dorsal root ganglion (DRG)

The cell bodies of sensory neurons are housed in the dorsal root ganglion (DRG). Compared to the somas of motor neurons, located in the spinal cord, the cell bodies of sensory neurons are more vulnerable to toxic insult due to the relatively permeable blood-nerve barrier at the DRG. The differences in blood-nerve barrier permeability between the DRG and spinal cord is thought to be in part responsible for the predominately sensory deficits observed in the clinical presentation of CIPN (McDonald et al. 2002).

Damage at the level of the DRG has been associated with several anticancer agents. Platinum compounds exert anticancer properties by binding to cellular DNA and consequently inducing cell death (Dasari et al. 2014). Concurrently, accumulation of platinum in the DRG has been observed (Krarup-Hansen et al. 1999, Ta et al. 2006), with the death of sensory neurons induced by platinum-DNA adducts being proposed as a primary mechanism for platinum-induced neuropathy (Ta et al. 2006, Dzagnidze et al. 2007). However, clinical improvement in
patients with platinum-induced neuropathy suggests that other, partially reversible mechanisms may also contribute to platinum-induced neuropathy (Argyriou et al. 2019).

**Axonal transport**

Microtubules are key structural elements in the nervous system and important in axonal transport. Disruption to microtubules contributes to the cytotoxic properties of cancer treatments including taxanes, however, microtubule interference may also be responsible for the neurotoxicity associated with these treatments (Jordan et al. 2004, Lapointe et al. 2013). The aggregation of microtubules can alter cell shape and stability, and disruption to microtubule dynamics can significantly interrupt axonal transport (Zajączkowska et al. 2019). Defective axonal transport impairs the delivery of materials and energy, contributing to the clinical manifestation of a length-dependent, ‘dying-back’ polynuclear neuropathy associated with these agents (Argyriou et al. 2019). Specifically, paclitaxel binds to and stabilises microtubules, potentially producing microtubule aggregations and leading to disruption in axonal transport (Bober et al. 2015).

**Mitochondrial dysfunction**

Impairment of energy mechanisms associated with mitochondrial dysfunction and generation of reactive oxygen species (ROS) may contribute to the primary neuropathy-inducing mechanisms of multiple neurotoxic agents. (Argyriou et al. 2019, Flatters et al. 2017). In addition to DNA-platinum adducts formed in the DRG, platinum compounds can also bind to mitochondrial DNA impairing physiological function, subsequently reducing cellular metabolism, and causing oxidative stress (Zheng et al. 2011, Di Cesare Mannelli et al. 2012). Similarly, depressed mitochondrial respiration following paclitaxel exposure has been demonstrated to occur selectively in the DRG, with cellular respiration remaining normal in the
ventral horn. This selective mitotoxic effect may also contribute to the sensory predominance of paclitaxel-induced neuropathy (Xiao et al. 2011).

**Ion channel dysfunction**

Acute neurotoxicity is a unique side effect of oxaliplatin treatment experienced by the majority of patients (Kokotis et al. 2016). The pathogenesis of this phenomena has been linked to the action of oxaliplatin on axonal membrane voltage-gated sodium (Na+) ion channel function and the subsequent peripheral nerve hyperexcitability (Sittl et al. 2012, Webster et al. 2005, Park et al. 2009a). Additionally, this acute modulation of Na+ channel properties in oxaliplatin treated patients has been demonstrated to impact the severity of chronic oxaliplatin induced neuropathy (Park et al. 2009a).

Some models of paclitaxel have also suggested the possibility of ion channel involvement in the pathogenesis of CIPN (Zhang et al. 2014, Aromolaran et al. 2017). However, unlike oxaliplatin-treated patients, human excitability studies have not identified alterations in sensory axon excitability indicative of ion channel dysfunction following paclitaxel exposure (Park et al. 2009a).

**OVERARCHING OBJECTIVES**

Oxaliplatin and taxane- treated cancer patients represent the largest cohorts of cancer survivors (Jemal et al. 2019), subsequently these cohorts are likely to experience long-term impacts from their neurotoxic cancer treatment. Furthermore, the number of cancer survivors living with long-term sequelae such as CIPN is likely to increase with continued implementation of successful cancer treatment with oxaliplatin and taxanes. Understanding the symptoms and
time course of CIPN are important factors for ensuring long-term quality of life in the cancer survivor population. However, targeting CIPN requires understanding of the CIPN phenotype and pathophysiological mechanisms underlying its development. Further, the link between patient symptoms and objective CIPN assessment remain ill-defined due to limitations of available assessment tools in translating patient experience into objective outcomes.

The aims of this thesis are to utilise robust multimodal assessment tools to characterise treatment specific CIPN profiles and explore patient characteristics which may contribute to CIPN severity. In total, this thesis will provide an improved understanding of CIPN associated with common cancer treatments and contribute to elucidating underlying mechanisms, develop CIPN vulnerability profiles which can inform the individualisation of treatment and provide the basis for future research into neuroprotection. Ultimately, the continued development and utilisation of novel measures quantifying CIPN will help to better inform treatment strategies and provide outcomes for clinical trials. Moreover, the identification of patient characteristics which may contribute to CIPN risk will assist in individualising treatment approaches to reduce the impact of CIPN in cancer survivors.
Chapter 2

Methodology
The methodology section below describes the general methods and patient cohorts used for studies in this thesis. Further specific details relating to clinical information, regimens, study specific methods and techniques are described in the main data chapters.

**Patient cohorts and clinical details**

Taxane and oxaliplatin treated cancer patients were referred for neurological assessment from Medical Oncology Departments at hospitals in Sydney and Brisbane (Chris O’Brien Life House, Prince of Wales Hospital, the Northern Cancer Institute, Sydney Adventist Hospital, the Mater Hospital and the Royal Brisbane and Women’s Hospital). Studies were approved by the Sydney Local Health District (RPAH Zone) and South Eastern Sydney Local Health District Human Research Ethics Committees according to testing location. All participants provided written informed consent in accordance with the declaration of Helsinki. Patients were over 18 years of age and presented with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. To gather a representative sample, no other specific exclusion criteria were applied.

Patients were referred for either prospective longitudinal studies at the commencement of oxaliplatin or taxane-based chemotherapy or for cross-sectional studies post completion of oxaliplatin or taxane-based chemotherapy. Prospective patients were assessed longitudinally, with baseline assessments occurring up to the second cycle of neurotoxic cancer treatment. Repeated assessments were conducted at mid and final treatment, with follow-up assessments at 3, 6- and 12-months post completion of neurotoxic chemotherapy (Fig 2.1). Cross-sectional patients underwent a single comprehensive neurotoxicity assessment 3 months-5 years post neurotoxic chemotherapy.

Patients were all prescribed standard chemotherapy-treatment regimens, with treatment modifications managed according to standard clinical practices if unacceptable toxicity developed. Weekly paclitaxel-treated patients were prescribed four cycles of Doxorubicin
(60mg/m²) and Cyclophosphamide (600mg/m²) every three weeks followed by 12 weekly cycles of paclitaxel (80 mg/m²) administered intravenously over 1 hour (Sparano et al. 2008). Three weekly paclitaxel (175 mg/m²) was administered intravenously over 3 hours in conjunction with 6 AUC of carboplatin for 4 to 6 cycles (Katsumata et al. 2009).

Patients receiving oxaliplatin-based treatment predominately received FOLFOX 6 regimen (Grothey et al. 2018, André et al. 2004), with oxaliplatin (85 mg/m²) given intravenously over 1 hour every 2 weeks in conjunction with leucovorin (50 mg) and followed by 5-fluorouracil (5-FU) administered via pump over 46 hours (2400 mg/m²). Treatment was prescribed for 12 cycles.

Figure 2.1. Schematic diagram of neuropathy assessments for cross-sectional and prospective patients.
Total Neuropathy Score (TNS © Johns Hopkins University)

Clinical neurological examinations were scored via the Total Neuropathy Score (Cavaletti et al. 2006, Cornblath et al. 1999). The Total neuropathy score clinical version (TNSc) consisted of 6 items (range:0-4): two symptom report and four items pertaining to clinical examination constituting vibration and pin prick sensibility, deep tendon reflexes and manual muscle testing (Table 2.1). Items were summed to give a composite score, with higher scores indicating greater severity of CIPN (TNSc, range 0-24). Neurophysiological measures, as described on page 10 were added to the TNSc to form the reduced version (TNSr, range 0-28; Table 2.1; item 7 and 8).

Firstly, patients were asked if they had experienced any changes of sensation such as numbness and tingling in their hands and feet and were graded based on how proximal the symptoms extended (Table 2.1; item 1). Additionally, patients reported if they had experienced any weakness in their arms and legs with grading based on the severity of the impairment (Table 2.1; item 2).

Examinations began at the distal extremities and continued proximally if impairment was evident (finger/toes→wrist/ankle→elbow/knee→above the elbow/knee). Neurotips (Owens Mumford, Woodstock, UK) were used to assess pin prick sensitivity based on the ability of patients to correctly distinguish between a sharp or blunt stimulus (Fig 2.2A). Examinations began in digit 2 and 5 of the dominant hand and contralateral foot. Impairment was graded if <9 out of 10 stimuli were correct, with testing continuing at the wrist/ankle. If less than 5/5 stimuli were correct at the wrist/ankle testing proceeded proximally and was graded accordingly (Table 2.1; item 3).

Examination of vibration-sensibility was conducted with a semi-quantitative Rydel-Seiffer tuning fork beginning at the interphalangeal joint of digit 1 (Fig 2.2B) of the dominant hand and contralateral foot. While averting their vision, patients indicated when they no longer detected vibration sensation. Vibration thresholds indicated on the tuning fork (0-8), were
sored against normative values (Martina et al. 1998), with examinations proceeded proximally if reduced vibration sensation was observed (Table 2.1; item 4). Manual muscle testing was conducted in the lower limb (Fig 2.2C; ankle dorsiflexion, toe flexion and extension) in line with standard protocols (Barbano 2000) and graded based on the severity of weakness (Table 2.1; item 5). Deep tendon reflexes at the ankle and knee (Fig 2.2D) were also conducted in line with standard clinical practice (Lees et al. 2019), with the bicep reflex also investigated in the absence of lower limb reflexes (Table 2.1; item 6).

Fig.2.2. Elements of total neuropathy score clinical neurological examination
### Table 2.1. Parameters of the Total Neuropathy Score

<table>
<thead>
<tr>
<th>Item</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Sensory symptoms</strong></td>
<td>None</td>
<td>Limited to fingers and toes</td>
<td>Extend to ankle or wrist</td>
<td>Extend to knee or elbow</td>
<td>Above knee or elbow</td>
</tr>
<tr>
<td><strong>2. Motor symptoms</strong></td>
<td>None</td>
<td>Slight difficulty mobilising</td>
<td>Moderate difficulty mobilising</td>
<td>Requires help or assistance</td>
<td>Paralysed</td>
</tr>
<tr>
<td><strong>3. Pin prick sensibility</strong></td>
<td>Intact</td>
<td>Reduced in fingers/toes</td>
<td>Reduced up to wrist/ankle</td>
<td>Reduced up to elbow/knee</td>
<td>Reduced above elbow/knee</td>
</tr>
<tr>
<td><strong>4. Vibration sensation</strong></td>
<td>Intact</td>
<td>Reduced in fingers/toes</td>
<td>Reduced up to wrist/ankle</td>
<td>Reduced up to elbow/knee</td>
<td>Reduced above elbow/knee</td>
</tr>
<tr>
<td><strong>5. Manual muscle testing</strong></td>
<td>Normal- can overcome resistance</td>
<td>Mild weakness- cannot overcome resistance</td>
<td>Moderate weakness- cannot overcome resistance but can move without resistance</td>
<td>Severe weakness- flicker of contraction when resistance eliminated</td>
<td>Paralysis- no contraction</td>
</tr>
<tr>
<td><strong>6. Deep tendon reflexes</strong></td>
<td>Normal</td>
<td>Ankle reflex reduced</td>
<td>Ankle reflex absent, knee reflex present</td>
<td>Ankle reflex absent, others reduced</td>
<td>All reflexes absent</td>
</tr>
<tr>
<td><strong>7. Sural nerve</strong></td>
<td>Normal or reduced to &lt;5% LLN</td>
<td>76-95% LLN</td>
<td>51-75% LLN</td>
<td>26-50% LLN</td>
<td>0-25% LLN</td>
</tr>
<tr>
<td><strong>8. Tibial nerve</strong></td>
<td>Normal or reduced to &lt;5% LLN</td>
<td>76-95% LLN</td>
<td>51-75% LLN</td>
<td>26-50% LLN</td>
<td>0-25% LLN</td>
</tr>
</tbody>
</table>

Total Neuropathy Score clinical version (TNSc) utilises item 1 to 6, with the total neuropathy score reduced version (TNSr) including items 7 and 8 (Cornblath et al. 1999, Cavaletti et al. 2006).
Tests of distal sensation

Von Frey monofilaments

Upper limb mechanical detection thresholds were evaluated bilaterally using Von Frey monofilaments (Optihair 2-Set, Marstock Nervtest, Germany, range: 0.125-512 mN) in digit 2 and 5 as a comparison of median and ulnar innervation. The weighted fibres with calibrated bending forces were applied perpendicular to the skin across five consecutive trials (Fig 2.3A). The weight was increased if the participant failed to identify the presence of the filaments on three of the five applications. Five trials were conducted using a series of ascending and descending stimulus intensities. A mechanical detection threshold (mN) was calculated using these trials in accordance with the scoring protocols (Rolke et al. 2006b).

Two-point discrimination

A two-point discriminator (Touch-Test® Two-Point Discriminator, North Coast Medical, Inc., California, USA model NC12776, range: 2 to 15 mm) was used to evaluate the cutaneous sensitivity of the sole of the first left metatarsus (Franco et al. 2012). The discriminator was positioned in an antero-posterior direction, perpendicular to the sole of the toe to ensure simultaneously contact of the points with the skin (Fig 2.3B). Pressure was applied until blanching and participants were asked to distinguish between one or two points. Two-point discrimination was tested ten times in a random order for each distance, with the smallest distance in which ≥70% correct trials were achieved being recorded.

Figure 2.3. A) Mechanical detection threshold being tested on digit 2 using Von Frey Monofilaments. B) Two-point discrimination being tested on the sole on the great toe.
Functional assessment

Grooved peg board test

Manual dexterity of the dominant hand was quantified by measuring the time (seconds) to place 25 grooved pegs into holes of varying orientation (Fig 2.4A). Patients were instructed to use only the dominant hand to insert one key at a time, proceeding from left to right filling the whole board. Patients performed two attempts which were averaged (Schmidt et al. 2000), with slower times indicative of worse hand functioning. Trials were ceased if not completed after five minutes.

Standing Balance

Lower limb functioning, indicated by standing balance was assessed via postural sway using a Swaymeter (Neuroscience Research Australia, Sydney; Fig 2.4B) (Mccrary et al. 2019a, Sturnieks et al. 2011). Patients with bare feet were asked to stand as still as possible, without talking for 30 seconds. The total movement of the centre of mass (mm) was measured via Swaymeter in stable (on the floor with eyes open and eyes closed) and unstable (on foam with eyes open and eyes closed) conditions. A sum score of the total path length from all four tasks was used for analysis, with longer postural sway path length indicating worse deficits (Mccrary et al. 2019b). Patients experiencing excess instability resulting in the termination of a condition were given a score equivalent to 3 standard deviations above the mean for that condition (Mccrary et al. 2019b).
Patient Reported Outcomes

FACT/GOG-Ntx questionnaire
Patients reported symptomatic CIPN burden via the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx, range:0-52) questionnaire. Neuropathy related items were scored on a 5-point scale (“Not at all” = 0, “A little” =1, “Somewhat” = 2 “Quite a bit” =3 “Very much” = 4) based on severity. Totals (out of 52) were reversed score in accordance with the manual (Calhoun et al. 2003, Webster et al. 2003), with lower scores indicating greater burden of symptoms. Patient reported neuropathy symptom severity was classified using the first two questions of the FACT/GOG-Ntx13 (Item 1: ‘I have numbness or tingling in my hands’ or Item 2: ‘I have numbness or tingling in my feet’ Range: 0-4). Patients reporting ‘Quite a bit’ (3) or ‘Very much’ (4) were classified as reporting severe numbness and tingling in the hands and feet. Patients reporting 1-4 on
Item 10 ‘I have trouble feeling the shape of small objects’ and 11 ‘I have trouble walking’ were classified as reporting functional impairment in the upper and lower limbs, respectively.

Semi-structured clinical interview

A semi-structured clinical interview (Bennett et al. 2007) was conducted to provide in-depth analysis of CIPN impact and symptoms. Patients were asked questions relating to the symmetry and distribution of neuropathic symptoms including “Describe any nerve symptoms you have experienced.”, “Are the symptoms worse in the hands or feet or are they equal?” and “Are the symptoms the same in the left and the right side in both the upper and lower limbs?”. Additionally, patients provided more details of the CIPN phenotype based on questions including “Have you had a greater than normal sense of touch”, “Are symptoms worse at any particular time of day?”, “Does anything make the symptoms worse?”. Questions relating to the impact of CIPN on sleeping (“Do you have trouble sleeping because of your symptoms?”) and other daily activities were also evaluated (“Are you off balance when walking?”, “Have you had any falls, slips or trips?”, “Does it affect your ability to exercise?”).

Nerve conduction studies

Bilateral nerve conduction studies (NCS) of the sural, tibial, median and ulnar nerves were collected using a Nicolet EDX Synergy (Natus Medical, Inc., Pleasanton, California) based on conventional techniques (Siao et al. 2011, Burke et al. 1974) Antidromic sural nerve compound sensory action potentials (CSAPs) were recorded at the lateral malleolus with the stimulation site 10–15 cm proximal. Tibial nerve compound muscle action potentials (CMAPs) were recorded from the abductor hallucis muscle, stimulating at the medial malleolus.

Upper limb CSAPs (Fig. 2.5) were recorded orthodromically from the median and ulnar nerves at the wrist, stimulating at digits 2 and 5, respectively. Median mixed palmers were recorded from the median nerve at the wrist stimulating 8cm distally in the palm between digit 2 and 3.
Recordings were also taken from the ulnar nerve, stimulating on the palm between digit 4 and 5 (Siao et al. 2011). Temperature was monitored and maintained at 32°C.

Values obtained from the sural, median, ulnar and tibial nerves were compared with the lower limit of age-matched normative ranges (Siao et al. 2011, Burke et al. 1974, Chen et al. 2016, Stevens 1997). Additionally, Sural CSAP and Tibial CMAPs were scored (Table 2.1 item 7 and 8) using the TNSr as described on page 52.
Figure 2.5. Upper limb nerve conduction studies with orthodromic recordings from the A) median and B) ulnar nerves. Median mixed palmer were recorded from the C) median and D) ulnar nerves, stimulating on the palm between digit 2/3 and 4/5 respectively.
Chapter 3

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Taxane-induced Peripheral Neuropathy: Differences in Patient Report and Objective Assessment
**Summary**

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting side-effect of neurotoxic cancer treatment impacting on long-term quality of life. Symptoms include numbness, tingling and pain, effecting the distal extremities. However, patients often report symptoms discrepant from the expected symmetrical distribution and the degree of concurrence with objective assessment remains ill-defined. This study aimed to investigate severity and symmetry of neuropathy symptoms to enable comparison of objective measures and patient report. 45 taxane-treated patients (F=43, 66±1.5 years, 19 months post-treatment) completed bilateral neuropathy assessments via clinical examination, sensory nerve conduction studies (NCS) and patient questionnaires. The laterality index (LI) was calculated as a ratio of smaller to larger side-to-side differences. Neuropathy was reported by 89% of the cohort. On clinical examination, 83% had ≥2 abnormalities, with 38-35% having upper or lower limb sensory amplitudes below normative range. 35% indicated side-to-side symptom asymmetry, however there was no significant asymmetry evident on clinical examination (LI Asym=.60±.10, Sym=.76±.05, NS) and no difference in side-to-side NCS (Median LI: Asym=.69±.06, Sym=.81±.04, NS; Sural LI: Asym=.80±.04, Sym=.81±.04, NS). Accordingly, there was no statistical association between patient reported and objective assessment of side-to-side asymmetry, suggesting discordance between patient experience and objective assessment. Similarly, discrepancies in symptom severity between hands and feet were reported by 32% of the cohort. However, patients reporting differences in symptom severity between the hands and feet were just as likely to present with comparable assessments as to demonstrate objective discrepancies. Discrepancies may exist between the patient experience of CIPN and objective assessments. Understanding these discrepancies may help to elucidate underlying mechanisms and better inform treatment strategies.
Introduction

Taxanes, including paclitaxel, abraxane, and docetaxel are used in the treatment of a range of cancers including breast, ovarian, cervical and prostate (Hennenfent et al. 2005). Chemotherapy-induced peripheral neuropathy (CIPN) is a major, dose-limiting side effect of taxane cancer treatment. Symptoms including paraesthesia, numbness and pain often interfere with patient function and typically present as a length-dependent, distal symmetric polyneuropathy (DSP) in a “glove and stocking” distribution (Park et al. 2013, Rowinsky et al. 1993).

Quantifying CIPN remains a challenge, due to a lack of agreement on ‘gold standard’ assessment and understanding of the pathophysiological mechanisms (Park et al. 2013, Alberti et al. 2014). Currently, clinician-based grading scales are primarily used to evaluate CIPN to inform dose modification and cessation decisions. However, these scales display poor sensitivity, low utility as a primary outcome in clinical trials and lack of concurrence with patient reports (Postma et al. 2005b, Brundage et al. 1993, Fromme et al. 2004, Basch et al. 2006).

Increasingly the patient perspective has been recognised as an important element for evaluating the impact of neuropathy (Hershman et al. 2011, Bennett et al. 2012), and as such patient-reported outcomes measures (PROMs) have been increasingly utilised in clinical trials to quantify the patient experience (Alberti et al. 2014). PROMs demonstrate concurrent validity with objective measures of neuropathy and can be combined with objective measures to enhance the measurement validity (Smith et al. 2018, Hershman et al. 2011). However, there remains a level of discord between the patient perception and clinical assessment (Alberti et al. 2014), especially at intermediate levels of neuropathy (Hershman et al. 2011). It is important to understand these discrepancies to identify quantitative and functionally relevant tools and elucidate pathophysiological mechanisms.
Although clinical research guidelines define DSP based on the presence of symmetrical and bilateral symptoms, signs, and abnormal nerve conduction studies (NCS) (England et al. 2005), anecdotally patients often report asymmetry in symptomatic expression of CIPN. To better understand discrepancies between patient reports of neuropathy and objective clinical and neurophysiology assessments, this study aimed to investigate the severity and distribution of neuropathy symptoms with a focus on symptom symmetry to enable comparison of objective measures and patient report.

**Methods**

**Patients**

Comprehensive assessments were conducted in patients who had received taxane-based treatment within the past 5 years. No patient reported symptoms of neuropathy prior to chemotherapy. One patient had diabetes, but without neuropathy. All patients provided written informed consent in accordance with the Declaration of Helsinki, with studies approved by the South Eastern Sydney Local Health District Human Research Ethics Committee.

**Assessment of neurotoxicity**

Neuropathy was bilaterally assessed via Total Neuropathy Score (©Johns Hopkins University) clinical version (TNSc) (Cavaletti et al. 2006) comprising of patient symptom report and neurological assessment, with greater CIPN severity indicated by a higher score (0-24).

Bilateral nerve conduction studies (NCS) of the sural, tibial, and median nerves were collected using a Nicolet EDX Synergy (Natus Medical, Inc., Pleasanton, California) as previously described (Siao et al. 2011, Burke et al. 1974). Lower limb NCS were added to the TNSc to provide the Total Neuropathy Score reduced version (TNSr).
The validated patient reported outcome questionnaire FACT/GOG-Ntx13 (Calhoun et al. 2003) was utilised to evaluate symptoms associated with chemotherapy-induced neuropathy range (0-52) (Webster et al. 2003), with lower scores indicating greater burden from neuropathic symptoms.

A semi-structured clinical interview (Bennett et al. 2007) was conducted to provide in-depth analysis of CIPN impact and symptoms. Patients were asked questions relating to the symmetry and distribution of neuropathic symptoms including “Describe any nerve symptoms you have experienced.”, “Are the symptoms worse in the hands or feet or are they equal?” and “Are the symptoms the same in the left and the right side in both the upper and lower limbs?”.

Data analysis

Results are presented as mean ± standard error of the mean (SEM) or median and interquartile range (IQR) where indicated. NCS were graded based on the lower limit of age matched normative ranges, established by an allied laboratory (Burke et al. 1974).

Discrepancies in reported symptom severity between hands and feet were graded based on a ≥2-point difference in severity between item 1 (“I have numbness or tingling in my hands”) and 2 (“I have numbness and tingling in my feet”) of the FACT/GOG-Ntx13. Objective scores were compiled based on TNSc vibration and pin prick sensibility components, conducted bilaterally in upper and lower limbs. Discrepancies based on these clinical components were defined as a ≥2-point difference between the upper and lower limb score.

Patients were classified as having either symmetrical or asymmetrical distribution based on their reports of side-to-side symptoms in the hands and feet. Those who described side-to-side asymmetry were further identified as having asymmetry in the upper limbs only, lower limbs only or both the upper and lower limbs. The side of greater severity was recorded as was patient handedness.
Scoring of the TNSc is based on the side with the greatest neuropathy symptom severity following bilateral examination. However, for the purpose of this study, items pertaining to patient symptom report (items 1 and 2) were removed from the TNSc score to provide a solely objective score based on clinical examination, with a ≥2-point difference between sides being classified as asymmetrical. A minimum score of 2 is required for neuropathy to be graded on the TNSc, therefore, a ≥2-point difference in the score was chosen to reflect either deficits in several clinical signs or more significant deficits in one modality between sides. The laterality index (LI) (Lo et al. 2008) was calculated as a ratio between the smaller and larger side-to-side values for the TNSc, sural and median nerve CSAPs, where values closer to 1 indicated greater symmetry.

The relationship between different assessments was determined using Pearson's correlations. Independent samples t-tests were conducted to assess the mean difference between patients reporting discrepancies in symptom severity (upper and lower limbs; side-to-side) and those reporting similar symptoms. Chi-square tests of independence were performed to examine the relations between patient reported and objective discrepancy. Fisher's exact tests were used where the assumptions of chi-square tests were violated. All statistics were performed in SPSS (Version 17, IBM) where significance was indicated as p ≤.05.

Results

Patient Characteristics

A total of 45 patients (43 female) underwent neurophysiological and clinical assessments at median of 19 months (IQR: 10-38 months) post taxane treatment. Most patients were treated with weekly paclitaxel (80mg/m2) for breast cancer (Table 3.1).
Table 3.1. Patient characteristics

<table>
<thead>
<tr>
<th>Demographic data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td><strong>Cancer type (n)</strong></td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Ovarian</td>
</tr>
<tr>
<td>Endometrial</td>
</tr>
<tr>
<td>Uterine</td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td><strong>Time since taxane treatment (months)</strong></td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Inter quartile range</td>
</tr>
<tr>
<td><strong>Taxanes Cumulative dose (mg/m²)</strong></td>
</tr>
<tr>
<td>Paclitaxel (n=41, weekly)</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Docetaxel (n=3, 3 weekly)</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Abraxane (n=1, weekly)</td>
</tr>
</tbody>
</table>
Assessment of Peripheral Neuropathy

Overall neuropathy symptom severity

The majority of the cohort (89%, n=40) reported symptoms of neuropathy, most often described as numbness (82%, n=37) and tingling (64%, n=29) in the distal extremities. Many patients described symptoms confined to the fingers and toes (33%, n=15), with no patients reporting symptoms extending past the elbows or knees. Of the total cohort, 71% (n=31) reported lower limb symptoms, with 29% (n=13) of patients reporting ‘quite a bit’ or ‘very much’ severity of tingling and numbness in their feet. 62% (n=27) reported upper limb neuropathy, with 13% (n=5) of patients reporting greater symptom severity.

On clinical examination, 83% (n=36) had ≥2 abnormalities, most commonly deficits in pinprick sensibility (91%, n=33) and deep tendon reflexes (83%, n=30), with vibration sensibility reduced in 41% of patients (n=18). Manual muscle testing was normal for most of the cohort (96%, n=41) consistent with preserved motor function. On NCS, 38% (n=25) of patients were below the lower limit of normative range for median compound sensory action potential (CSAP) amplitude (Burke et al. 1974) (LLN; Table 2), suggestive of axonal dysfunction. Similarly, sural CSAPs were below the LLN for 35% (n=15) of patients. However, tibial compound motor action potential (CMAP) amplitude was below normative range in only 9% (n=4), indicative of minimal motor involvement.
Table 3.2. Neuropathy characteristics

<table>
<thead>
<tr>
<th>Entire cohort (n = 45)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT/GOG-Ntx13 score (mean ± SE; range)</td>
<td>41.7 ± 0.1 (27 - 51)</td>
</tr>
<tr>
<td>Median CSAP (mean ± SE; µV)</td>
<td>10.08 ± 0.92</td>
</tr>
<tr>
<td>Sural CSAP (mean ± SE; µV) 41–60-year age group</td>
<td>14.25 ± 1.53</td>
</tr>
<tr>
<td>Sural CSAP (mean ± SE; µV) 61–80-year age group</td>
<td>8.17 ± 0.82</td>
</tr>
<tr>
<td>Tibial CMAP (mean ± SE; mV)</td>
<td>8.68 ± 0.71</td>
</tr>
</tbody>
</table>

Upper/lower limb symptom severity

<table>
<thead>
<tr>
<th>Different (%, n)</th>
<th>28.9 (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT/GOG-NTX13 score (mean ± SE)</td>
<td>42.1 ± 1.3</td>
</tr>
<tr>
<td>Median CSAP (mean ± SE; µV)</td>
<td>8.85 ± 1.31</td>
</tr>
<tr>
<td>Sural CSAP (mean ± SE; µV)</td>
<td>9.16 ± 1.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Similar (%, n)</th>
<th>62.2 (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT/GOG-NTX13 score (mean ± SE)</td>
<td>39.9 ± 1.5</td>
</tr>
<tr>
<td>Median CSAP (mean ± SE; µV)</td>
<td>10.59 ± 1.19</td>
</tr>
<tr>
<td>Sural CSAP (mean ± SE; µV)</td>
<td>10.10 ± 1.02</td>
</tr>
</tbody>
</table>

Side-to-side symptom symmetry

<table>
<thead>
<tr>
<th>Symptom asymmetry (%, n)</th>
<th>31.1 (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT/GOG-NTX13 score (mean ± SE)</td>
<td>39.8 ± 1.3</td>
</tr>
<tr>
<td>Sural laterality index</td>
<td>0.80 ± 0.04</td>
</tr>
<tr>
<td>Median laterality index</td>
<td>0.69 ± 0.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom symmetry (%, n)</th>
<th>57.8 (26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT/GOG-NTX13 score (mean ± SE)</td>
<td>41.5 ± 1.4</td>
</tr>
<tr>
<td>Sural laterality index</td>
<td>0.78 ± 0.05</td>
</tr>
<tr>
<td>Median laterality index</td>
<td>0.81 ± 0.04</td>
</tr>
</tbody>
</table>
Deficits in the combined clinical and electrodiagnostic examination (higher TNSr score) demonstrated a significant correlation with patient reported symptom burden (lower FACT/GOG-Ntx13 score, \( r=-.342, p<.05 \)), suggesting moderate agreement between patient reported neuropathy burden and objective examination.

Discrepancies in symptom severity between the upper and lower limbs

Discrepancies in symptom severity between the hands and feet were reported by 32\% (n=13) of the cohort. Greater symptom severity was typically described in the feet (n=12), consistent with a length dependent neuropathy. However, those reporting symptom discrepancy did not report overall greater neuropathy symptom burden than those reporting equal symptom severity between hands and feet (N.S. Table 3.2). Similarly, sensory NCS did not differ significantly between the groups (Fig.1A; Table 3.2), suggesting similar axonal function.
Figure 3.1A. Mean sural (grey) and median (black) CSAP compared between those reporting differences in symptom severity between the hands and feet and those reporting equivalent symptom severity. **B)** The proportion of patients who reported differences in symptoms severity between hands and feet (≥2-point difference item 1 and 2 of the FACT/GOG-Ntx13) indicated in grey and those who reported comparable symptoms between the hands and feet (<2 point difference) indicated in black, with either comparable (<2 points) or discrepant (≥2-points) objective neuropathy assessment.
On clinical examination, 49% (n=20) of the total cohort demonstrated discrepancies in objective assessment between the hands and feet, with greater deficits in the feet. Those with discrepancies on clinical examination did not differ in overall neuropathy severity (TNSc=4.65 ±.41) compared to those with similar assessments (TNSc= 3.86 ±.60, N.S), suggesting upper and lower limbs discrepancies were not reflecting greater overall neuropathy severity.

Of the 49% (n=20) of patients who demonstrated upper and lower limb discrepancies in objective clinical assessment, only 30% (n=6) reported discrepancies in symptom severity. However, a similar number of patients (n=7) with comparable clinical examinations reported discrepancies in symptom severity between the hands and feet (Fig.3.1B). Accordingly, there was no statistical association between patient reported and objective assessment of symptom discrepancy between the hands and feet ($X^2 (1, N = 41) = .05, N.S$), suggesting that patients reporting discrepancies in symptom severity were not more likely to present with discrepancies in objective assessment.

**Side-to-side asymmetry**

Of the patients reporting neuropathy symptoms (n=40), 35% (n=14) indicated side-to-side symptom asymmetry 28.5% (n=4) upper limbs only, 43% (n=6) lower limbs only and 28.5% (n=4) both upper and lower limbs. For those describing upper limb asymmetry (n=8), the majority reported worse symptoms in the dominant handed side (n=6). Patients describing side-to-side asymmetry did not report greater overall neuropathy symptom burden compared to those with symmetrical distribution (N.S, Table 3.2). Similarly, there was not greater objective evidence of clinical neuropathy in patients reporting asymmetrical side-to-side symptoms (TNSc) with patient reported items removed (LI: asymmetrical=.60±.10, symmetrical=.76±.05, N.S.) or difference in side-to-side NCS (N.S., Fig. 3.2A; Table 3.2).
**Figure 3.2A.** Mean laterality index of sural (grey) and median (black) amplitudes for those reporting side-to-side symmetry and asymmetry in symptom severity. **B)** The proportion of patients who reported side to side asymmetry in symptoms severity, indicated in grey and those reporting symmetrical symptoms indicated in black with either comparable (<2-point difference in bilateral TNSc scores) or discrepant (≥2-points) objective neuropathy assessment.
Of the total cohort, 29% (n=13) had a ≥2-point discrepancy in bilateral TNSc scores once the patient reported items were removed, with pin prick sensibility contributing most significantly asymmetrical clinical scores (≥2-point, 22%, n=10). Other signs were less frequently asymmetrical in isolation (≥2), however deep tendon reflexes (≥2-point, n=1, 1-point difference n=12) and vibration sensibility (≥2-point, n=1, 1-point difference n=7) most frequently contributed to the asymmetrical score, with asymmetrical weakness contributing the least (≥2-point, n=0, 1-point difference n=1). Those with objective side-to-side asymmetry did not differ in overall neuropathy severity (TNSc= 4.15 ±.63) compared to those with symmetrical assessments (TNSc= 4.25±.40, N.S), suggesting asymmetry did not reflect greater overall neuropathy severity. Similarly, deficits in objective examination were not associated with handedness, time since treatment completion or age (N.S).

Of the 29% (n=13) of the cohort who demonstrated side-to-side asymmetry in objective clinical assessment, only 46% (n=6) reported side-to-side asymmetries in symptom severity consistent with objective assessment. However, a similar number of patients with symmetrical objective assessments also reported asymmetry in symptom severity (n=8, Fig.3.2B). Accordingly, there was no statistical association (p=.286) between patient reported and objective assessment of side-to-side asymmetry, suggesting discordance between patient experience and objective quantification of neuropathy.

Discussion

This study compared objective measures and patient reports of CIPN, through the exploration of neuropathy symptom severity, symmetry, and distribution. Reflective of previous studies, persistent symptomatic and objective neuropathy was evident for a large number of patients following taxane treatment (Hershman et al. 2011, Argyriou et al. 2005a), highlighting neuropathy as a long-term sequela which may be detrimental to quality of life in cancer survivors. However, considerable discrepancies in reported symptoms between upper and lower limbs and from side-to-side was identified. Further, despite moderate global
agreement, discrepancies were evident between the patient experience and objective assessments of CIPN.

Based on established clinical definitions (Argyriou et al. 2005a, Tzatha et al. 2016), symmetrical signs and symptoms of CIPN with greater deficits in the feet were expected. Consistent with this description (England et al. 2005), 32% of patients reported varied symptomatic expression of CIPN between the hands and feet, with 49% demonstrating discrepancies between the upper and lower limbs in objective clinical assessment. Similar reports of worse chronic neuropathy in the lower limbs have been reported previously in taxane-treated (Ventzel et al. 2016, Pachman et al. 2016) and mixed groups of patients with CIPN (Wolf et al. 2012). Interestingly, during paclitaxel treatment, patients reported similar levels of neuropathy in hands and feet, however post-treatment symptoms in the hands were more likely to resolve (Pachman et al. 2016). Similarly, in the present cohort, patients reported greater residual severity of symptoms in the feet. Likewise, deficits in clinical examination were more often observed in the lower limbs. However, a similar percentage of patients were below the lower limit of normal for both median and sural nerve CSAPs, with no differences in NCS between those reporting similarities in symptom severity in the hands and feet and those reporting differences.

In contrast to the expected pattern of symmetric neuropathy, 35% of patients reporting symptoms described side-to-side asymmetry, with 29% of the cohort demonstrating bilateral differences on objective clinical assessment. However, objective evidence of asymmetry was not identified in clinical or neurophysiological assessments in those reporting asymmetrical side-to-side symptoms. Asymmetric NCS responses have previously been observed in taxane-treated patients (Chen et al. 2013). However, analyses were conducted retrospectively from a population investigated for severe neuropathy and accordingly, the clinical population differs from the present study. Other reports have identified asymmetry in symptom report and clinical examination or vibration or tactile function in taxane (Zhi et al. 2019) and
ixabepilone-treated patients (Goel et al. 2008). However, asymmetric clinical examination
was not directly compared with patient report to reveal discrepancies.

Further, there was no statistical association between patient reported and objective
assessment of symptom asymmetry in the present study. Alberti et al. previously reported
discrepancies between patient report and objective assessments of CIPN, which were most
pronounced in patients with moderate neuropathy (Alberti et al. 2014). This discordance
between the patient experience and objective quantification of neuropathy could suggest that
current objective assessments lack the sensitivity to fully quantify the expression of CIPN, thus
patient reports reflect subtle neurophysiologic changes yet to be defined. However, the
disparities between the patient experience and objective measures could also suggest that
patients are adapting to their symptoms and demonstrating clinical and symptomatic recovery
in the context of limited neurophysiological recovery (Kandula et al. 2017). This adaptive
process could be potentially targeted as a strategy to ameliorate the impact of CIPN.

Previous findings emphasize the importance of including PROMs for a patient-centred
assessment of CIPN, gaining insight into symptom burden and quality of life (Park et al.
2017a, Alberti et al. 2014). Consequently, PROMs have been used as primary outcome
measures in CIPN clinical trials (Smith et al. 2013, Kautio et al. 2009). However, inconsistencies
between the patients’ interpretation of questions and the intended meaning, as well as the
possibility that patients have a lower and more varied interpretation of severity have been
highlighted as potential limitations of PROMs (Lavoie Smith et al. 2017, Hertz 2019).
Moreover, although patients provided the best information about how neuropathy affects their
daily lives, this may not translate into an appropriate standard to classify severe cases in a
clinical trial setting (Hertz 2019). Additionally, the tendency for patients in the current
investigation to report side-to-side asymmetry consistent with the side of dominant
handedness, may suggest a perceptual based bias. Psychological factors, such as anxiety,
have also been shown to be significantly associated with patient reports of persistent
neuropathy symptoms (Ventzel et al. 2016, Lee et al. 2018), suggesting that reported neuropathy symptoms may require review in the context of the entire individual, including the evaluation of psychological factors.

Conversely, objective discrepancies were not associated with handedness, time since treatment completion, or age. Objective neurological examinations and neurophysiological measures have demonstrated superior ability in predicting final outcome in CIPN (Alberti et al. 2014, Velasco et al. 2010b, Argyriou et al. 2008), providing evidence of early physiological changes prior to symptom onset and identifying those at risk of severe neurotoxicity (Argyriou et al. 2008, Park et al. 2009a, Park et al. 2009b, Velasco et al. 2014). As such, objective measures, particularly neurophysiological techniques have been recommended as preferential for understanding pathophysiological mechanisms and determining the efficacy of potential neuroprotectants (Kandula et al. 2017, Argyriou et al. 2019), as well as potentially informing strategies such as dose reduction or omission of neurotoxic agents. Despite this, there remains a lack of implementation of neurophysiology in the clinical trials setting (Kandula et al. 2017).

In total, this analysis has provided evidence of the variability in clinical presentation of taxane-induced neuropathy. It remains unclear if the patient perspective or objective quantification of CIPN most accurately represents the underlying pathophysiology of CIPN. While patient reports provide insight into the clinical impact of CIPN, objective measures may provide more mechanistic information. This study highlights the importance of incorporating both kinds of measures for primary end points in clinical trials as well evaluation of CIPN symptoms in a clinical setting. Further, our findings highlight the variability in symptom report and that a substantial minority of patients may report symptoms that are discrepant with the expected symmetrical distribution of toxic neuropathy. Understanding the patterns and significance of CIPN symptoms is critical both to improve toxicity assessment and to examine the implications on long-term quality of life in cancer survivors.
Chapter 4

Electrophysiological and Phenotypic Profiles of Taxane-induced Neuropathy
Summary

This study aimed to comprehensively describe patient-reported, functional and neurophysiological outcomes to elucidate the phenotypic profile of taxane-induced neuropathy. Taxane-treated patients (n=47) completed cross-sectional bilateral clinical and sensory assessments and nerve conduction studies. Patients reported symptom severity via Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx13) questionnaire. Symptoms of neuropathy were reported by 81% of patients. On clinical examination, 62% had 2 or more abnormalities, with 20% indicating significant symptomatic and objective neuropathy. Nerve conduction studies were consistent with a sensory predominant axonal neuropathy. However, features more typical of entrapment neuropathy were also present in >50%, which were not associated with overall severity of CIPN or clinical risk factors. There is considerable variation in CIPN phenotypes associated with taxane-treatment. Understanding their clinical associations may assist in identification of patients at risk of severe neurotoxicity. This would enable treatment modification decisions but also limit early cessation of effective anti-cancer treatment in patients with less severe neurological sequelae. Understanding the CIPN phenotype may inform treatment decisions which could impact clinical and survival outcomes.
Introduction

Cancer survivorship has dramatically increased over the past 20 years, with over 48 million cancer survivors worldwide (Jemal et al. 2019). Breast cancer survivors represent the largest cohort of female cancer survivors (Jemal et al. 2019). Accordingly, it is imperative that potential long-term side effects of cancer treatment for breast cancer are understood. Up to 80% of breast cancer patients are estimated to experience chemotherapy-induced peripheral neuropathy (CIPN) following taxane treatment, with 30% having severe symptoms (Rowinsky et al. 1993, Hershman et al. 2011, Park et al. 2013).

CIPN typically produces predominantly sensory neuropathy, leading to functional impairment with walking, balance, and fine motor function. Classically, symptoms are bilateral and symmetrical (England et al. 2005). Neurophysiological features are typical of a predominately sensory axonal neuropathy (Argyriou et al. 2008), with abnormalities commonly identified in the sural nerve (Rutkove et al. 1997, Bromberg et al. 1993). However, the CIPN phenotype may be complicated in breast cancer patients by other risk factors for nerve damage including adjuvant treatment with radiotherapy, aromatase inhibitors and surgery, as well as the presence of lymphedema (Stubblefield et al. 2015, Bozentka et al. 2001, Sestak et al. 2009, Delanian et al. 2012).

Currently, clinical impression is used in the oncology setting to evaluate CIPN and subsequently inform modification or discontinuation of anticancer treatment. Cessation of effective treatment may impact overall survival, especially in the adjuvant setting where clinical outcomes are dependent on dose intensity (Denduluri et al. 2018). Moreover, there remains a lack of consensus regarding a gold standard assessment tool for CIPN (Alberti et al. 2014, Park et al. 2013, Argyriou et al. 2019) with subsequent discrepancies in identifying affected patients. As CIPN is an expected side-effect with no effective preventative strategies, patients may not report specific details of neurological symptoms. Similarly, clinicians may not correctly distinguish the
pattern of symptoms leading to possible misdiagnosis. It is important to recognise the spectrum of clinical and electrophysiological features of CIPN to identify patients at risk of severe neurotoxicity. The present study aimed to investigate the phenotypic profile of neuropathy following taxane treatment with a focus on comprehensively describing patient reported, functional and neurophysiological outcomes.

**Methods**

**Patients**

Patients who had completed taxane-based cancer treatment within the past five years were identified by their treating oncologist and referred for clinical and neurophysiological assessments. Medical history, including treatment (lymph node dissections, radiotherapy, aromatase inhibitors), previous diagnosis of carpal tunnel syndrome, lymphoedema, diabetes and pre-existing neuropathy symptoms was collected. Studies were approved by the South Eastern Sydney Local Health District Human Research Ethics Committee and written informed consent was obtained in accordance with the Declaration of Helsinki.

**Assessment of neurotoxicity**

**Patient reported outcomes**

Neuropathy burden was assessed using the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx1, range:0-52) questionnaire with lower combined reversed scores indicating greater symptomatic burden (Calhoun et al. 2003, Webster et al. 2003). Patients were classified based on item 1 (I have numbness or tingling in my hands) and 2 (I have numbness or tingling in my feet) of the FACT/GOG-Ntx13 into those who had none- mild symptoms in the hands or feet (score 0-2) vs those with more severe symptoms in the hands or feet (3-4). Distribution and location of
neuropathy symptoms were further evaluated by a semi-structured clinical interview (Bennett et al. 2012).

Electrophysiological studies

Nerve conduction studies (NCS) were conducted in the upper and lower limbs bilaterally using a Nicolet EDX Synergy device (Natus Medical, Inc., Pleasanton, California) as described in the methods section. Briefly, lower limb NCS consisted of antidromic sural sensory nerve action potentials (SNAPs), and tibial nerve compound muscle action potentials (CMAPs).

Upper limb SNAPs were recorded orthodromically from the median and ulnar nerves. Mixed palmers were recorded from the median and ulnar nerve at the wrist (Siao et al. 2011). Values obtained from the sural, median, ulnar, and tibial nerves were compared with the lower limit of age-matched normative ranges (Siao et al. 2011, Burke et al. 1974, Chen et al. 2016, Stevens 1997). Temperature was monitored and maintained at 32°C.

Clinical examination

Neuropathy was clinically assessed bilaterally using the Total Neuropathy Score clinical version (TNSc © Johns Hopkins University) a validated composite measure, comprising of patient symptom report and neurological assessment including examination of vibration and pin prick sensation, deep tendon reflexes and manual muscle testing (Cavaletti et al. 2006, Cornblath et al. 1999). Higher scores indicated greater severity of CIPN (range 0-24). Neurotips (Owens Mumford, Woodstock, UK) were used to assess pin prick sensitivity based on ability to correctly distinguish between a sharp and blunt stimulus. Discrepancies in hypoalgesia between ulnar and median innervated sensory territories were defined as a ≥2-point difference in pin prick sensibility between digit 2 and digit 5.
Upper limb mechanical detection thresholds were evaluated bilaterally using Von Frey monofilaments (Optihair2-Set, Marstock Nervtest, Germany) in digit 2 and 5 as a comparison of median and ulnar innervation.

A two-point discriminator (Touch-Test® Two-Point Discriminator, North Coast Medical, Inc., California, USA model NC12776, range: 2 to 15 mm) was used to evaluate the cutaneous sensitivity of the sole of the first left metatarsus (Franco et al. 2012).

Lower limb NCS (tibial, sural amplitudes) were graded against normative ranges and added to the TNSc and summed into the Total Neuropathy Score reduced version (TNSr © Johns Hopkins University; range 0-32) (Cavaletti et al. 2006, Cornblath et al. 1999), with the cohort being classified as having mild (1-2), moderate (3-4), severe (5-8) or very severe (≥9) CIPN (Park et al. 2011b). Symptoms, signs and NCS taken from the TNSr was used to estimate the likelihood of DSP based on established consensus criteria (England et al. 2005).

Data analysis

Results are presented as the mean with standard error or median with interquartile range (IQR) where appropriate. The relationship between different assessments was determined using Pearson’s correlations. Wilcoxon signed rank test was used to determine difference between digit 2 and digit 5 in mechanical detection thresholds for each patient with the most affected limb being utilised for analysis (Chen et al. 2013, Bland 2000, England et al. 2005). Differences between patients with and without median and sural nerve abnormalities were analysed using Mann-Whitney U tests, with Chi-square tests of independence being performed to examine the relationship with patient reported neuropathy symptoms. Fisher’s exact tests were utilised to examine the relationship of median nerve abnormalities and abnormal nerve conduction studies where the assumptions of chi-square tests were violated. Univariate analysis revealed the association between clinical characteristics and median nerve
abnormalities. All statistics were performed in SPSS (Version 17, IBM) where significance was indicated as $p \leq 0.05$.

**Results**

**Patient characteristics**

Cross-sectional bilateral neurological assessments were conducted in 47 patients (45 females, Table 4.1) at a median of 19 months (IQR: 10-38 months) post-taxane treatment. The majority had received weekly paclitaxel (80mg/m²) for breast cancer, with 11 receiving aromatase inhibitors. None of the cohort reported symptoms of neuropathy prior to chemotherapy treatment.

**Table 4.1. Patient characteristics**

<table>
<thead>
<tr>
<th>Demographic data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>Mean ± SE</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td><strong>Cancer type % (n)</strong></td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Ovarian</td>
</tr>
<tr>
<td>Endometrial</td>
</tr>
<tr>
<td>Uterine</td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td><strong>Time since taxane treatment (months)</strong></td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Inter quartile range</td>
</tr>
<tr>
<td><strong>Taxanes Cumulative dose (mg/m²)</strong></td>
</tr>
<tr>
<td>Paclitaxel (n=41, weekly)</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Docetaxel (n=3, 3 weekly)</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Abraxane (n=1, weekly)</td>
</tr>
</tbody>
</table>
Patient reported phenotypes

The majority of patients reported neuropathic symptoms at the time of assessment (80.9%, n=38), all of whom described numbness as a primary symptom, followed by tingling (61.7%, n=29) and less frequently pain (23.4%, n=11). The overall FACT score indicated that patients were experiencing mild to severe neuropathy symptom burden (mean: 41.80±.93, range:27-51). Of the cohort, 70.2% (n=33) reported symptoms of neuropathy in the lower limbs, with 29.8% (n=14) reporting ‘quite a bit’ or ‘very much’ severity. Neuropathy in the upper limbs was reported by 59.6% (n=28) of the cohort, with 10.6% (n=5) reporting greater severity. The reported distribution of neuropathy symptoms in the hands was consistent with a DSP with the exception of two patients (4%) who reported symptoms in a distribution more typical of median nerve entrapment (localisation to the palmar aspects of digit 1, 2 and 3 (Siao et al. 2011).

Electrophysiological profile

Mean SNAP amplitudes were below the lower limit of normal (LLN) in 23-30% of the cohort (Table 4.2; Fig. 4.1), with mean tibial CMAP amplitude and latency only abnormal for 4.4% of patients consistent with sensory predominance. Similarly, ulnar, median and sural SNAP latencies were normal for 93.5-97.8% of the cohort, consistent with axonal neuropathy. Unexpectedly, prolonged median mixed palmer’s latencies and increased median to ulnar mixed palmar latency differences were present in >50% of the cohort, with 29.5% demonstrating slowed median SNAP conduction velocities (CV), features more typical of a median nerve entrapment neuropathy (Table 4.2; Fig.4.1).
Figure 4.1. Percentage of patients with abnormal nerve conduction study parameters; CV: Conduction Velocity; SNAP: Sensory Nerve Action Potential; CMAP: Compound Motor Action Potential
Table 4.2. Electrophysiological profile

<table>
<thead>
<tr>
<th>NCS parameter</th>
<th>Mean ±SE (Entire cohort)</th>
<th>Normal value</th>
<th>Total cases</th>
<th>Abnormal cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median SNAP latency</td>
<td>2.68±.08 ms</td>
<td>≤3.5ms</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Median SNAP CV</td>
<td>48.10±1.53 m/s</td>
<td>≥44 m/s</td>
<td>44</td>
<td>13</td>
</tr>
<tr>
<td>Median SNAP amplitude</td>
<td>9.71±.89 µV</td>
<td>(19-49 years) ≥11µV</td>
<td>46</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(50-79 years) ≥ 7 µV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulnar SNAP latency</td>
<td>2.08±.10 ms</td>
<td>≤3.1 ms</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Ulnar SNAP CV</td>
<td>48.55±1.16 m/s</td>
<td>≥45 m/s</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>Ulnar SNAP amplitude</td>
<td>6.91±.44 µV</td>
<td>(19-49 years) ≥11uV</td>
<td>39</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(50-79 years) ≥ 5 uV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median mixed palmers' latency</td>
<td>1.93±.06 ms</td>
<td>≤1.8 ms</td>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>Transcarpal Median to Ulnar Palmar latency difference</td>
<td>0.51±.09 ms</td>
<td>&lt;0.4 ms</td>
<td>37</td>
<td>19</td>
</tr>
<tr>
<td>Sural SNAP latency</td>
<td>2.47±.09 ms</td>
<td>≤3.6 ms</td>
<td>45</td>
<td>1</td>
</tr>
<tr>
<td>Sural SNAP amplitude</td>
<td>9.78±.91 µV</td>
<td>(61-80 years) ≥6µV</td>
<td>45</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(41-60 years) ≥7µV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibial latency</td>
<td>4.32±.13 ms</td>
<td>≤6.1ms</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td>Tibial CMAP amplitude</td>
<td>8.90±.72 mV</td>
<td>≥3mV</td>
<td>45</td>
<td>2</td>
</tr>
</tbody>
</table>

CV: Conduction Velocity; SNAP: Sensory Nerve Action Potential; CMAP: Compound Motor Action Potential
Figure 4.2. Patients scores on the Total Neuropathy Score reduced version (TNSr) a composite grading measure of clinical, neurophysiological and patient reported neuropathy and the likelihood of the distal polyneuropathy being present based on consensus criteria.

Clinical presentation and neurological phenotype

On clinical examination, 62% (n=30) had 2 or more abnormalities most often occurring in the lower limb. Distal loss of pin-prick sensibility (72.3%, n=34) and reduction or absence of ankle reflexes (74.5%, n=35) were most common. Vibration sensibility was reduced in the distal extremities for 15 patients (44.1%), with only mild weakness present for two patients, consistent with a length-dependent sensory predominant neuropathy. Furthermore, upper limb vibration
sensibility was intact for all patients, with deficits in pin prick sensibility most frequently observed in the lower limbs. Similarly, lower limb tactile spatial acuity evaluated by two-point discrimination revealed significant impairment, with 37% (n=17) of patients being unable to discriminate between one or two points at the upper limit (15mm), suggesting significant hypoalgesia in the lower limb.

A Wilcoxon signed rank test demonstrated a significant difference (Z = -3.7, p< 0.001) in upper limb mechanical detection threshold, assed using Von Frey monofilaments, between median innervated (median digit 2: .18 mN, IQR:.15-.54) and ulnar innervated regions (median digit 5: .15, IQR:.12-.18). With, 19.6% (n=9) of patients demonstrated pin prick discrepancies (≥2-points) between digit 2 and digit 5, though increased hypoalgesia in digit 2 was only evident for 6 patients.

Of the cohort, 60% (n= 27) had a TNSr score ≥5 (Fig. 4.2), indicating a significantly symptomatic and objective neuropathy (Park et al. 2011b), with 20% (n=9) demonstrating severe neuropathy (TNSr ≥9). However, according to consensus criteria (England et al. 2005) which require combined deficits in symptoms, signs and NCS, only 26% of patients met the requirements for having a high likelihood of DSP, suggesting a level of discord with the clinical definition of CIPN (Fig. 4.2).

**Associations between clinical and electrophysiological phenotypes**

Patients with sural SNAP amplitudes below the LLN (n=13) did not report overall greater symptom burden (Mann-Whitney U= 152.5, N.S.; Table 4.3), but were more likely to report symptoms of neuropathy in the feet (X² (1, N = 47) = 4.1, p<.05) and present with greater deficits on clinical examination (TNSc: Mann-Whitney U=72.0, p<.001.; Table 4.3). However, there were no differences between individual components of the TNSc including vibration and pinprick sensibility or deep tendon reflexes (N.S., Table 4.3), highlighting the potential limitations of using single measures. Similarly, patients with median SNAP amplitudes below
LLN (n=14) also did not report overall greater symptom burden (Mann-Whitney U= 150.5, N.S, Table 4.3), or show greater deficits in pinprick or vibration sensibility (Table 4.3, N.S), despite presenting with greater deficits on the total score (TNSc, Mann-Whitney U=142.5 p<.05, Table 4.3). However, unlike those with lower limb deficits, these patients were not more likely to report symptoms in the hands compared to those with normal median SNAP amplitudes ($X^2 (1, N = 46) = .02, N.S$).

Patients presenting with additional median nerve abnormalities (CV, mixed palmar's latency, median to ulnar palmar latency difference), could not be distinguished from those without based on reported neuropathy symptoms in the hands ($X^2 (1, N = 47) = .05, N.S$). Median nerve abnormalities were not more likely to occur with abnormal median ($X^2 (1, N = 47) = 3.55, N.S$) or sural SNAP amplitudes ($X^2 (1, N = 47) = .12, N.S$). Furthermore, median nerve abnormalities were not associated with overall severity of CIPN assessed via clinical examination, patient report or electrophysiological criteria (Median CV: $r= -.122$, Median mixed palmar's latency: $r= .164$, Median to ulnar palmar latency difference: $r= .211$, N.S).

In addition, there was no significant association between clinical risk factors and median nerve abnormalities (radiation treatment, aromatase inhibitor use, diabetic status, age, time since taxane treatment, previous CTS, upper limb lymphoedema, N.S.).

**Discussion**

The present study comprehensively described patient reported, functional and neurophysiological outcomes to elucidate the phenotypic profile of neuropathy following taxane treatment. We identified significant symptomatic and objective neuropathy in the majority of the cohort. In addition to neurophysiological findings supporting an axonal sensory neuropathy, features more consistent with an entrapment neuropathy involving the median nerve were also frequently observed in the cohort. Suggestive of more distal upper limb involvement than expected for a strict length dependent pattern.
Consistent with the clinical definition of axonal neuropathy (Rutkove et al. 1997), the majority of the cohort reported symptoms suggestive of large fibre sensory neuropathy, most commonly affecting the feet. These findings are consistent with previous studies demonstrating greater persistence of neuropathic symptoms in lower limbs post-treatment (Pachman et al. 2016). Similarly, reduction in sural SNAP amplitudes have been reported amongst taxane-treated cohorts (Argyriou et al. 2005b, Sahenk et al. 1994) and demonstrated to be predictive of the final neurological outcomes following paclitaxel treatment (Argyriou et al. 2005b). Abnormal sural NCS in the context of relatively preserved median nerve responses is typically expected in neuropathic disorders where length-dependent involvement predominates (Bromberg et al. 1993). However, a similar proportion of patients in the current study also demonstrated reductions in median SNAP amplitudes. Similar findings have been reported previously in paclitaxel-treated patients (Augusto et al. 2008, Pachman et al. 2016). Accordingly, reduced median SNAP amplitudes in the absence of upper limb symptoms may reflect symptomatic recovery in the context of limited neurophysiological improvement (Kandula et al. 2017).

We identified sural SNAP amplitudes below the lower limit of normal in 29% of patients. However, normative ranges for electrodiagnostic examinations are typically broad, reflecting the broad range of sensory amplitudes across healthy individuals. Accordingly, patients who have undergone significant axonal loss may still demonstrate normal NCS as highlighted in prior studies in paclitaxel-treated patients (Pace et al. 1997, New et al. 1996). Patients with reduced median or sural SNAP amplitudes in this study did not differ in overall patient reported symptom burden compared to those with normal NCS. The combination of clinical examination and patient report improved the ability to distinguish patients with abnormal NCS from those within normative ranges. These results highlight the importance of including both patient report and multimodal clinical examination in conjunction with neurophysiological assessment (Alberti et al. 2014, Argyriou et al. 2019).
In this study and contrary to the expected electrodiagnostic profile, median nerve abnormalities with demyelinating features were evident in >50% of patients. These abnormalities were not reflected in the patient reported severity or distribution of neuropathy symptoms in the hands or difference in semi-quantitative sensory testing between ulnar and median innervated regions. Median nerve abnormalities demonstrated in the current study were not associated with overall neuropathy severity assessed via clinical examination, patient report or electrophysiological criteria and therefore are unlikely to be a manifestation of secondary demyelination associated with severe CIPN (Argyriou et al. 2008).

A retrospective analysis of NCS from taxane-treated patients referred for severe neuropathy revealed similar median nerve abnormalities (Chen et al. 2013). The authors suggested that electrodiagnostic features indicative of median nerve abnormalities might reflect a mononeuropathy that may manifest with taxane treatment. There is some evidence that mononeuropathies are more common in patients with generalised polyneuropathy such as diabetic neuropathy (Rota et al. 2016, Rinkel et al. 2018), suggesting that functional impairment and structural changes may result in a greater vulnerability to entrapment. In addition, carpal tunnel syndrome (CTS) is the most common upper limb mononeuropathy (Soumaya et al. 2016) and has been associated with multiple conditions and comorbidities (Solmaz et al. 2016). Moreover, the population of breast cancer patients who receive taxanes as part of their treatment may be at higher risk of nerve entrapment due to other treatment related complications (Ganel et al. 1979, Nishihori et al. 2008, Burns 1978). However, the current study revealed no association between median nerve abnormalities and clinical factors including radiation treatment, aromatase inhibitor uses or upper limb lymphoedema. However, the lack of association between clinical factors and median nerve abnormalities should be verified in a larger population.

Estimates of median nerve abnormalities in the general population vary (Atroshi et al. 1999, Ferry et al. 1998, De Krom et al. 1992), mostly due to a lack of consensus on diagnostic
criteria, standard assessment protocols and normative values. In cohorts of breast cancer patients treated with aromatase inhibitors, a CTS prevalence of 11% was identified with symptom questionnaires (Sheng et al. 2019) and 2.7% with electrophysiological confirmation (Soumaya et al. 2016). As such, comparing the prevalence of median nerve abnormalities in the current cohort to a related population is difficult. However, future prospective studies should monitor the development and determine the significance of these abnormalities in the context of the phenotypic profile of chronic taxane-induced neuropathy.

*Implications in the clinical setting*

This study highlights the spectrum of CIPN phenotypes and discrepancies which may exist between clinical presentations and classic definitions of length-dependent axonal neuropathy. Greater understanding of the complete spectrum of CIPN phenotypes in taxane-treated patients is important to guide assessment strategies and identification of patients with severe symptoms. In the absence of neuroprotective strategies, dose modification or early cessation is the only available option for clinicians to limit the impact of neuropathy. Accordingly, appropriate identification of patients at risk of severe neurotoxicity is important to enable dose modification while limiting premature cessation of effective cancer treatment in patients with less severe neurological sequelae.
Chapter 5

Weekly Paclitaxel-induced Neurotoxicity in Breast Cancer: Outcomes and Dose Response
Summary

Paclitaxel treatment for breast cancer produces significant peripheral neuropathy but the time course of neuropathy development and neuropathy outcomes are unclear. Although dose reduction is the only strategy to prevent neurotoxicity, the impact of dose-reduction on neuropathy outcomes following treatment remains unknown. This study aimed to prospectively evaluated neuropathy development and deficits from weekly paclitaxel treatment and evaluate the impact of dose-reduction on post-treatment neuropathy outcomes.

Patients with breast cancer receiving paclitaxel (80mg/m²) weekly for 12-weeks were prospectively recruited (pre cycle 1 paclitaxel). Comprehensive patient reported (FACT/GOG-Ntx13) clinical (TNSc) and neurophysiological measures were utilised to assess neuropathy development and recovery up to 12-months post completion (n=83). The impact of dose-reduction on post-treatment clinical and patient reported neuropathy outcomes (assessed at 3.6 ± 0.1 months post-treatment) was evaluated in 105 weekly paclitaxel-treated patients.

Significant neuropathy was present by 6 weeks across patient-reported, clinical, and objective neurophysiological assessments, increasing in prevalence and severity over the treatment course, peaking at 12 weeks with 85.5% of patients reporting symptoms in the hands and/or feet. Limited recovery occurred during follow-up, with significant neuropathy compared to baseline being maintained up to 12 months (p<.05). Neuropathy was a dose-limiting side effect in 36.2% of patients. Patients who received dose reduction had worse patient reported (FACT/GOG-Ntx13:40.2±1.4) and clinical neuropathy outcomes (TNSc:4.3±0.4) compared to those who received the full dose (FACT/GOG-Ntx13:45.9±0.9; TNSc:3.3±0.3, p<.05). three months post-treatment. Patients who ceased treatment early (cumulative paclitaxel dose: 582.1±29.9 mg/m²) demonstrated worse deficits (TNSc:5.0 ±0.6; FACT/GOG-Ntx13: 37.3±2.7) compared to those who received the complete dose (960 mg/m²; TNSc: 3.5 ±0.3; FACT/GOG-Ntx13: 45.3±0.9, p<.05).

Weekly paclitaxel produces symptomatic and objective neuropathy early in the treatment course which can persist. Dose reduction does not necessarily lead to more favourable neuropathy outcomes, with individual risk factors likely important in addition to cumulative dose.
**Introduction**

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating side effect of neurotoxic cancer treatment. Estimated to occur in up to 80% of paclitaxel-treated breast cancer patients (Hershman et al. 2011, Sparano et al. 2008), neuropathy symptoms can interfere with function, increasing the risk of falls (Winters-Stone et al. 2017) and reducing quality of life (Rowinsky et al. 1993, Hershman et al. 2011, Park et al. 2013). However, despite a high incidence, patient impact and outcomes remain poorly understood. Many prior studies of CIPN have lacked comprehensive quantitative CIPN assessment measures, sufficient follow-up time and treatment homogeneity (Rivera et al. 2017), limiting their ability to provide clinically useful prognostic information.

Paclitaxel-induced CIPN has a major impact on treatment tolerability, resulting in dose reduction and early cessation (Rowinsky et al. 1993, Perez 1998). Approximately 25% of breast cancer patients receive reductions to their adjuvant paclitaxel treatment due to CIPN (Speck et al. 2013), which may affect clinical and survival outcomes. Dose-reduction is the only current strategy to mitigate CIPN and relies on accurate identification of CIPN symptoms. However, CIPN can be challenging for clinicians to identify, evaluate and manage. As there is no consensus on a gold standard CIPN assessment tool (Smith et al. 2018, Loprinzi et al. 2020, Mccrary et al. 2017) and no defined objective thresholds or pharmacokinetic parameters to identify risk of CIPN (Hertz 2019, Salgado et al. 2020), clinicians depend on clinical experience to provide the maximum effective dose while ensuring patient quality of life. However, accurately identifying patients at-risk of severe neuropathy remains a challenge, and neuropathy outcomes for those who receive dose-reduction remain ill defined.

Weekly paclitaxel administration has become the most commonly utilised regime for adjuvant treatment of early breast cancer, demonstrating superiority over other schedules in both disease-free progression and overall survival (Sparano et al. 2008). However, the incidence
and severity of paclitaxel induced CIPN has been linked to increased cumulative dose and the frequency of exposure, with those receiving weekly administration demonstrating greater neuropathy than other schedules (Sparano et al. 2008, Pace et al. 2007, Seidman et al. 2008). Given that the 5-year survival rate for early breast cancer patients is >90% (Australian Institute of Health and Welfare, 2019), the impact of CIPN on function and quality of life is a significant consideration for this population. A comprehensive understanding of the clinical manifestations and outcomes of weekly paclitaxel-induced neuropathy may provide clinicians with resources to better inform treatment decisions and counsel patients (Pachman et al. 2015). Accordingly, this study prospectively evaluated neuropathy development and deficits in patients with breast cancer during weekly paclitaxel treatment. Further, we evaluated the impact of dose-reduction on post-treatment clinical and patient-reported neuropathy outcomes.

Methods

Patients and study design

Patients with breast cancer who were prescribed monotherapy with 80mg/m² paclitaxel weekly for 12 weeks undertook comprehensive clinical and neurophysiological assessments. Patients were included if they had no evidence of pre-existing polyneuropathy or any prior neurotoxic chemotherapy treatment. During the course of the study, no patients received additional neurotoxic chemotherapy such as platinum agents or additional lines of taxane-based therapy. However, patients were able to receive non-neurotoxic cancer treatment such as trastuzumab. Written informed consent was obtained in accordance with the Declaration of Helsinki, with studies approved by the Sydney Local Health District Human Research Ethics Committee and South Eastern Sydney Local Health District Human Research Ethics Committee.

Eighty-three patients were prospectively recruited prior to cycle 1 of paclitaxel for a longitudinal analysis of the natural progression and recovery of paclitaxel-induced peripheral
neuropathy. Patients were assessed at baseline (week 0), mid-treatment (week 6), final
treatment (week 12) and post-treatment at 3, 6 and 12 months. With follow-up assessments
only conducted in patients who did not recommence neurotoxic treatment. In addition, twenty-
three patients who had completed weekly paclitaxel cancer treatment underwent a one-off
cross-sectional assessment post-paclitaxel completion (Table 5.1, Fig.5.1). Cross-sectional
evaluations were undertaken between 3 to 6 months post-completion of paclitaxel treatment.
Cross-sectional patients were comparable to the prospectively recruited cohort in terms of
cumulative dose, age and neuropathy severity based on patient report and clinical
examination (Table 5.2). To analyse the impact of dose reduction, cross-sectionally assessed
patients were analysed together with data from prospectively assessed patients at the 3 or 6-
month post-paclitaxel completion time-point, for a total of 105 paclitaxel-treated breast
cancer patients.

**Dosing information**

Demographic and paclitaxel dose data was collected from medical records. Dose reductions
or cessations were recorded with the reason for the modification. Patients were classified as
having either ‘no dose reduction’, ‘reduction due to peripheral neuropathy ’or ‘reduction due to
other causes’. Patient who discontinued treatment prior to receiving all 12 prescribed cycles
were classified as ceasing early (ceasing between cycle 6-9) or late (ceasing between cycle
10-11) in the treatment course.
### Demographic data

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Mean ± SE (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean ± SE (Range)</td>
<td>52.7 ± 1.2 (28 – 76)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>Mean ± SE (Range)</td>
<td>27.8 ± .64 (18.6 – 51.4)</td>
</tr>
<tr>
<td><strong>Diabetes (n, %)</strong></td>
<td></td>
<td>7 (6.7%)</td>
</tr>
<tr>
<td><strong>Prescribed CIPN treatment (n, %)</strong></td>
<td></td>
<td>9 (8.6%)</td>
</tr>
<tr>
<td><strong>Breast cancer stage (n, %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
<td>6 (5.7%)</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>47 (44.8%)</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>37 (35.2%)</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>7 (6.7 %)</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>8 (7.6%)</td>
</tr>
<tr>
<td><strong>Receptor status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER positive</td>
<td></td>
<td>71 (67.6%)</td>
</tr>
<tr>
<td>PR positive</td>
<td></td>
<td>58 (55.2%)</td>
</tr>
<tr>
<td>HER2 positive</td>
<td></td>
<td>27 (25.7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>3 (2.85%)</td>
</tr>
<tr>
<td><strong>Time since taxane treatment (months)</strong></td>
<td></td>
<td>3.57±1.6 (2-8)</td>
</tr>
<tr>
<td><strong>Cumulative paclitaxel dose (mg/m²)</strong></td>
<td></td>
<td>Mean ± SE (Range)</td>
</tr>
<tr>
<td>Prospective cohort (n=83)</td>
<td></td>
<td>861.8±15.9 (474-960)</td>
</tr>
<tr>
<td>Whole cohort (n=105)</td>
<td></td>
<td>848.9±14.8 (400-960)</td>
</tr>
<tr>
<td>No dose modification (n=53)</td>
<td></td>
<td>960.0±0</td>
</tr>
<tr>
<td>Any dose modification (n= 52)</td>
<td></td>
<td>736.0±20.0 (400-940)</td>
</tr>
<tr>
<td>Type</td>
<td>Mean (SE)</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>Early cessation (6-9 cycles) (n=19)</td>
<td>582.1±29.9 (400-720)</td>
<td></td>
</tr>
<tr>
<td>Late cessation (10-11 cycles) (n= 25)</td>
<td>817.8 ±12.6 (660-880)</td>
<td></td>
</tr>
<tr>
<td>No treatment discontinuation (n=61)</td>
<td>944.7±5.6 (760-960)</td>
<td></td>
</tr>
</tbody>
</table>

**Reason for Dose modification (n, %)**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>38 (36.2%)</td>
</tr>
<tr>
<td>Other#</td>
<td>14 (13.3%)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SE, standard error.

# Neutropenia or thrombocytopenia (n=3), fluid retention (n=2), patient travel (n=2), abnormal liver function (n=1), arthralgias (n=1), cardiovascular concerns (n=1), diarrhea (n=1), fever (n=1) and unspecified (n=2)

^Patient taking medication to treat CIPN at time of assessment including pregabalin and gabapentin
**Figure 5.1. Consort diagram**

- **Patient recruitment**
  - Patients recruited pre cycle 1 paclitaxel (n= 83)
  - 0 weeks (n= 83)
  - 6 weeks (n= 77)
  - 12 weeks (n=69)
  - 3 months (n= 71)
  - 6 months (n= 68)
  - 12 months (n= 56)

- **Treatment duration**

- **Follow-up**

- **Analysis**
  - Neuropathy development and recovery (n= 83)

- **Patients recruited cross-sectionally (n= 23)**
  - Evaluate the impact of dose-modification on neuropathy outcomes (n= 105)
Table 5.2 Comparison between prospective and cross-sectional cohorts.

<table>
<thead>
<tr>
<th></th>
<th>Age (Years)</th>
<th>Cumulative paclitaxel dose (mg/m²)</th>
<th>Total Neuropathy Score clinical version</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
</tr>
<tr>
<td><strong>Cross-sectional (n=23)</strong></td>
<td>57.4±2.4</td>
<td>802.9±36.0</td>
<td>4.57±.65</td>
</tr>
<tr>
<td><strong>Prospective (n=82)</strong></td>
<td>51.2±1.3</td>
<td>861.8±15.9</td>
<td>3.57±.27</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mann-Whitney U</td>
<td>Mann-Whitney U</td>
<td>Mann-Whitney U</td>
</tr>
<tr>
<td></td>
<td>=664.5 p=0.31</td>
<td>=732.0 p=0.80</td>
<td>=778.0 p=0.20</td>
</tr>
</tbody>
</table>

There was no difference in age, cumulative dose or neuropathy based on patient report and clinical examination, between patient recruited prospectively or cross-sectionally. As such both sets of patients were included in the analysis evaluating the effect of dose modification on follow-up neuropathy outcomes.

**Assessment of neurotoxicity**

Neuropathy burden was assessed via the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx13, range:0-52), a validated patient reported outcome measure (PROM) (Calhoun et al. 2003, Webster et al. 2003). Lower scores were associated with greater symptomatic burden, with a 10% reduction in scores from baseline being considered clinically significant (Hershman et al. 2018). The Total Neuropathy Score clinical version (TNSc© Johns Hopkins University), a validated composite measure of patient symptom report and neurological assessment was used to clinically assess neuropathy (Cavaletti et al. 2006, Cornblath et al. 1999), with higher scores indicating greater neuropathy severity (range:0-24) (Cavaletti et al. 2006, Cornblath et al. 1999).

Nerve conduction studies (NCS) were undertaken as previously described (Timmins et al. 2020a), recording compound sensory nerve action potential (CSAP) amplitudes from the sural...
nerve. Specific tests of distal sensation were performed using Von Frey monofilaments in the upper limb and two-point discrimination in the lower limb.

**Statistical analysis**

Generalised estimating equations (Liang *et al.* 1986), were utilised to evaluate the progression of neuropathy over time. Results are presented as predicted mean estimate of change from baseline (week 0). An exchangeable correlation structure was used to account for repeated measures. Baseline sural NCS were added as a covariate to account for the variation in starting values. 2-tailed Mann-Whitney U tests were conducted to confirm that those with missing data at 12 months post-treatment did not differ significantly in dose, age or neuropathy severity (Table 5.3). To evaluate the impact of dose-reduction non-parametric data was analysed using 2-tailed Mann-Whitney U tests to investigate the differences between patients with respect to dosing. Chi-square tests of independence were used to examine relationships with symptom severity. Statistical analysis was performed using SPSS (Version 17, IBM) with statistical significance set at $p \leq 0.05$ and results presented as mean with standard error, unless otherwise specified.
Table 5.3 Follow-up group comparison

<table>
<thead>
<tr>
<th></th>
<th>Age (Years)</th>
<th>Cumulative paclitaxel dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
</tr>
<tr>
<td>Follow-up at 12 months</td>
<td>51.1±1.5</td>
<td>845.1±20.6</td>
</tr>
<tr>
<td>(n=56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Follow-up at 12</td>
<td>51.2±2.4</td>
<td>899.9±21.4</td>
</tr>
<tr>
<td>months (n=27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>Mann-Whitney U</td>
<td>Mann-Whitney U =589.0 p=.74</td>
</tr>
<tr>
<td></td>
<td>=753.0 p=.977</td>
<td></td>
</tr>
</tbody>
</table>

There was no significant difference in cumulative dose or age between those who had a follow-up assessment at 12 months post-treatment (n=56) and those who do not (n=27)

Results

Development and recovery profile of weekly paclitaxel-induced peripheral neuropathy

The natural history of neuropathy development and recovery was documented using comprehensive, multimodal assessment tools. Weekly paclitaxel-treated patients (n=83, Table.5.1) underwent baseline assessment (week 0), with further assessments carried out after 6±0.1 and 12±0.2 weeks of treatment (Fig.5.1). Follow up assessments were conducted at 3±0.2, 6±0.1 and 12±0.2 months post-completion of paclitaxel treatment.

Development of neuropathy

Based on scores from the FACT/GOG-Ntx13, 54.5%, (n=42) reported numbness and tingling in the hands by week 6 of treatment, with 13% (n=10) reporting 'quite a bit' or 'very much'. Similarly, 58.4%, (n=45) reported symptoms in the feet, with 13%, (n=10) reporting greater severity (Fig.5.2a). Interestingly, some patients were already reporting functional deficits, such
as difficulty feeling the shape of small objects (14.3%, n=11) and problems with walking (11.7%, n=9, Fig.5.2b).

Concurrently, overall patient reported neuropathy burden increased, with a decline in FACT/GOG-Ntx13 scores (lower scores indicating worse neuropathy) of 4.1 points (Table 5.4) by week 6. Objective evidence of neuropathy also developed by week 6, with a mean increase in total neuropathy scores consistent with mild neuropathy (Park et al. 2011b) (1.9 points, \( p<.05 \), Fig.5.3a). Similarly, a significant reduction in sural amplitude (-3.0μV, \( p<.05 \), Table 5.4) was also evident by 6 weeks, suggestive of early axonal dysfunction.
Figure 5.2a. The percentage of patients reporting any (solid) numbness and tingling in the hands and feet and those reporting greater severity of symptoms in the hands and feet (dash).

Figure 5.2b. The percentage of patients reporting functional impairments in the upper limb (difficulty manipulating objects) and lower limb (problems walking) during paclitaxel treatment (0-12 weeks) and post completion (3-12 months).
Table 5.4. Mean estimates of the change in neuropathy outcomes since the beginning of paclitaxel treatment (week 0)

<table>
<thead>
<tr>
<th></th>
<th>FACT/GOG-Ntx13</th>
<th>TNSc</th>
<th>CSAP Sural amplitude (µV)</th>
<th>Two-point discrimination (mm)</th>
<th>Von Frey (mN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
</tr>
<tr>
<td>Week 0 (n=83)</td>
<td>49.4 48.7 50.1</td>
<td>1.2±.2* .91 1.5</td>
<td>18.7 16.4 20.9</td>
<td>8.4 7.8 9.1</td>
<td>.37 .29 .45</td>
</tr>
<tr>
<td>Week 6 (n=77)</td>
<td>-4.1±.6* -5.2</td>
<td>-2.8 1.9±.2* 1.4</td>
<td>-3.0±.8* -4.7</td>
<td>-1.4 0.3±.4 -0.5</td>
<td>1.0 .26±.16 .14</td>
</tr>
<tr>
<td>Week 12 (n=69)</td>
<td>-9.7±.9* -11.5</td>
<td>-7.9 3.6±.3* 2.9</td>
<td>-5.7±1.0* -7.7</td>
<td>-3.8 1.6±.5* 0.7</td>
<td>2.5 .60±.21 .18</td>
</tr>
<tr>
<td>3 Months post treatment (n=71)</td>
<td>-5.0±.8* -6.5</td>
<td>-3.5 2.4±.3* 1.8</td>
<td>-4.9±1.9* -6.7</td>
<td>-3.1 2.2±.5* 1.3</td>
<td>3.1 .31±.14 .04</td>
</tr>
<tr>
<td>6 Months post treatment (n=68)</td>
<td>-4.8±.8* -6.4</td>
<td>-3.2 1.9±.3* 1.4</td>
<td>-3.9±1.1* -6.1</td>
<td>-1.8 1.7±.5* 0.8</td>
<td>2.5 .33±.21 -.08</td>
</tr>
<tr>
<td>12 Months post treatment (n=55)</td>
<td>-4.8±.8* -6.4</td>
<td>-3.2 1.8±.2* 1.1</td>
<td>-2.9±1.2* -5.2</td>
<td>-0.5 2.2±.5* 1.3</td>
<td>3.1 .37±.36 -.34</td>
</tr>
</tbody>
</table>

Mean estimates of change from the predicted mean at week 0, presented with standard error and 95% confidence intervals. *Indicates significant the change from week 0 (p<.05). Predicted means for other measured are presented in appendix 1.


CSAP Sural amplitude: Compound sensory nerve action potential amplitude measured from the sural nerve. Baseline Sural amplitude was added a covariate to improve the fit of the model.

Two-point discrimination: Larger distance (mm) indicate greater sensory deficit. Von Frey monofilament: Higher force (mN) indicates greater sensory deficit.
Consistent with patient reports of neuropathy symptoms in the hands, distal sensation in the upper limbs had worsened significantly from baseline (week 0) with an increase in mechanical detection threshold of .26mN ($p<.05$, Table 5.4). However, there were no significant changes observed in lower limb sensation (two-point discrimination) from baseline after 6 weeks of paclitaxel (Table 5.4, Fig.5.3b).

After completing 12 weeks of treatment, 85.5%, (n=59) of patients reported numbness and tingling in their hands, with 82.6%, (n=57) reporting symptoms in their feet. Correspondingly, more patients reported severe symptoms (hands: 30.4%, n=21; feet 37.7%, n=26 Fig.5.2a) and functional impairment (difficulty manipulating objects 30.4%, n=21; problems with walking 37.7%, n=26, Fig.5.2b).

Overall patient-reported symptom burden also peaked in severity at the end of 12 weeks of paclitaxel, with the average change from baseline representing a clinically significant deficit (Hershman et al. 2018) (-9.7 points, $p<.05$, Table 5.4). Consistent with patient reported symptom burden, objective neuropathy scores also increased maximally from baseline (3.6 points, $p<.05$ Fig.5.3a) as did sensory deficits in the upper limbs (.60mN, $p<.05$, Fig.5.3b). Lower limb sensation also demonstrated significant deficits compared to baseline with increased detection threshold (1.6mm, $p<.05$, Fig. 5.3b). Similarly, sensory nerve amplitudes demonstrated the greatest decline from baseline (-5.7 µV, $p<.05$, Table 5.4).

Recovery profile

Following completion of weekly paclitaxel treatment, there was some evidence of symptomatic recovery, with a reduction in the proportion of patients reporting neuropathy symptoms at 3 months post completion, compared to week 12. However, 57.7% (n=41) of patients reported residual neuropathy in the hands and 62% (n=44) in the feet, with more patients reporting greater severity of symptoms in the feet (33.8%, n=24) compared to the hands (18.3%, n=13).
Figure 5.3a. Predicted means and 95% confidence intervals for the Total Neuropathy Score clinical version (TNSc; higher scores in FACT/GOG-Ntx13 indicate greater neuropathy severity) and patient reported neuropathy burden (score; lower scores indicate greater neuropathy burden). Assessments collected during treatment (weeks) and at post completion (months).

Figure 5.3b. Predicted means and 95% confidence intervals for von Frey monofilaments (mN) performed in the upper limb and two-point discrimination (mm) performed in the lower limb. Great values indicating greater deficits. Assessments collected during treatment (weeks) and at post completion (months).
Functional difficulties were reported by 31% (n=22) of patients in the hands and by 23.9% (n=17) with walking (Fig. 5.2b).

Six months after paclitaxel completion, approximately half the cohort still reported neuropathy symptoms (hands: 47.1%, n=32; feet: 55.9%, n=38), which were maintained up to 12 months post-completion (hands: 50.9%, n=28; feet: 52.7%, n=29, Fig. 5.2a). Severe symptoms in the feet were still reported by 26.5% (n=18) of patients at 6 months and 18.1% (n=10) at 12 months. However, fewer patients reported severe neuropathy symptoms in the hands (6 months: 14.7%, n=10, 12 months: 5.5%, n=3), suggesting greater symptomatic improvement in the upper limbs (Fig. 5.2a).

Correspondingly, deficits in lower limb sensation (two-point discrimination) increased maximally from baseline at 3 months (2.2mm, p<.05) and were maintained up to 12 months post-completion (2.2mm, p<.05, Fig. 5.3b). However, by 6 months post-completion, changes in upper limb sensation (Von Frey monofilaments) were no longer significantly different from baseline (6 months: 0.33mN 95%CI: -.08 to .74mN; 12 months: 0.37mN, 95%CI: -.34 to 1.1mN, N.S., Table 5.2), suggesting variations in the pattern of neuropathy recovery between upper and lower limbs (Fig. 5.3).

Compared to the end of treatment (12 weeks), some improvement was seen in overall patient-reported neuropathy burden, however deficits remained clinically significant from baseline (FACT/GOG-Ntx13: -5.0 points, p<.05, Table 5.4) and did not improve over the 12-month follow-up period (6 and 12months: -4.8 points, p<.05, Fig. 5.3a).

Similarly, despite some improvement, TNSc scores remained significantly elevated from baseline at the 3-month (2.4 points, p<.05), 6-month (1.9 points, p<.05) and 12-month follow-up assessments (1.8 points, p<.05, Table 5.4). Correspondingly, sural nerve conduction studies showed continued deficits from week 0 up to 12-months post completion (-2.9µV, p<.05, Table
suggesting incomplete recovery of objective and symptomatic neuropathy by 12 months post treatment.

**Dose reduction and neuropathy outcomes**

To evaluate the effect of dose reduction on neuropathy outcomes, 105 breast cancer patients (Table 5.1) were assessed cross-sectionally 3.6 ± 0.1 months post-paclitaxel treatment. In total, 49.5% (n=52) of these patients experienced paclitaxel dose reduction, with neuropathy accounting for 73.1% of these reductions (n=38, Table 5.1). In total, 36.2% of the cohort required dose reduction for neuropathy (n=38). The dose reduction group received lower cumulative paclitaxel dose (736±20 mg/m² vs 960 mg/m², p<.01), with those discontinuing treatment early (n=19) in the course receiving the lowest dose (582.1±29.9 mg/m², Table 5.1).

At follow-up, residual neuropathy was reported in 77% (n= 40) of patients who had received any dose reduction and 70% (n=37) who received the full dose, with those receiving dose reduction more likely to report ‘quite a bit’ or ‘very much’ numbness and tingling in the hands or feet (X²(1,n= 105) =4.29, p<.05).

Those receiving dose reduction demonstrated significantly greater deficits, based on clinical grading (TNSc: 4.3±0.4) compared to those who received the full dose (TNSc: 3.3±0.3, Mann-Whitney U=1063, p<.05). Concurrently, patient reported symptom burden was significantly worse for patients who received a reduced dose (FACT/GOG-Ntx13 dose reduction: 40.2±1.4; full dose: 45.9±0.9, Mann-Whitney U=876, p<.05). However, there were no significant differences in specific tests of distal sensation in the upper or lower limbs (N.S.).

Treatment was discontinued for 18% (n=19) of patients early in the course (6-9 cycles), with the majority of these ceasing due to neuropathy (79%, n=15). Patients requiring early cessation had significantly worse neuropathy based on clinical grading (TNSc: 5.0 ±0.6, Mann-Whitney U=388.5, p<.05, Fig. 5.4a) and reported greater overall neuropathy burden.
Figure 5.4a. Total neuropathy score clinical version for patients who ceased treatment early (cycle 6-9) or late in the treatment course (cycle 10-11) compared to those who completed 12 cycles of paclitaxel. *P<.05. Higher scores indicate greater neuropathy severity.

Figure 5.4b. FACT/GOG-Ntx13 for patients who ceased treatment early (cycle 6-9) or late in the treatment course (cycle 10-11) compared to those who completed 12 cycles of paclitaxel. *P<.05. Lower scores indicate greater neuropathy severity.
(FACT/GOG- Ntx13: 37.3±2.7, Mann-Whitney U= 341, p<.05, Fig. 5.4b) compared to those who received all cycles regardless of dose reduction (n=61, TNSc:3.5 ±0.3; FACT/GOG-Ntx13: 45.3±0.9). However, these differences in patient report and clinical examination were not evident for those who ceased paclitaxel late in the treatment course (10-11 cycles, n=25), with outcomes being comparable at follow-up (TNSc: 3.5 ±0.6, Mann-Whitney U =743, N.S; FACT/GOG-Ntx13: 42.2±1.9, Mann-Whitney U =622.5 N.S) to those who did not discontinue treatment (n=61, Fig.5.4a,5.4b). Similarly, those discontinuing early demonstrated significantly worse distal sensation in the lower limbs (two-point discrimination: 12.3±0.9mm) compared to those who did not cease treatment (9.76±0.6mm, Mann-Whitney U=262, p<.05) but upper limb sensation did not differ between groups.

**Discussion**

This study used comprehensive multimodal assessment to assess neuropathy development and evaluate recovery up to 1-year post completion in a homogenous cohort of weekly paclitaxel treated patients. Across patient reported, clinical, and objective neurophysiological assessments, significant neuropathy was already present by 6 weeks of treatment, increasing in prevalence and severity over treatment. Limited recovery occurred during follow-up, with significant neuropathy being maintained up to 12months, with deficits more pronounced in lower limbs. Moreover, neuropathy was a significant dose-limiting side effect with more than a third of patients requiring dose reductions due to neuropathy. Three months after treatment, patients who received dose reduction had worse patient-reported and clinical neuropathy outcomes, with those ceasing treatment early demonstrating the most deficits, despite receiving the lowest cumulative dose.

**CIPN phenotype associated with weekly paclitaxel administration**

Weekly paclitaxel treatment regimens form a key foundation of the treatment of early-stage breast cancer (Sparano et al. 2008, Fujii et al. 2015). Neuropathy is a well-recognised toxicity...
of weekly paclitaxel treatment— with significant ≥grade 2 CIPN reported in 27% of patients (Sparano et al. 2008). Our study identified symptoms of CIPN of any severity in 85% of weekly paclitaxel-treated patients, with severe symptoms in 38%. This is a similar range to other studies examining CIPN with weekly paclitaxel (Park et al. 2011a, Kuroi et al. 2009, Pace et al. 2007), although rates of CIPN vary considerably depending on the specific assessment method used.

More than half the cohort reported numbness and tingling after 6 weeks, with some patients already describing severe symptoms and functional deficits. This finding was supported by clinical examination and significant reduction in sural amplitude from baseline, suggestive of early axonal dysfunction. Neuropathy peaked at the end of treatment, in terms of incidence, severity and functional deficits. Similar to previous reports, neuropathy severity in the hands and feet were similar during treatment (Pachman et al. 2016). However, greater symptomatic improvement was seen in the upper limbs. Lower-limb predominance is consistent with length dependent neuropathy (Timmins et al. 2020b, Park et al. 2013) and may support the role of disrupted axonal transport as a potential mechanism of paclitaxel-induced neuropathy.

A critical feature of the present study is the high proportion of patients experiencing symptoms at 12 months post paclitaxel completion. Despite some improvement from the end of treatment, patient reported symptom burden remained clinically significant at 12 months post-completion, in-line with previous reports of the persistence of paclitaxel-induced peripheral neuropathy (Pachman et al. 2016, Hershman et al. 2018, Bandos et al. 2018). However, in contrast to platinum-induced peripheral neuropathy, there was no evidence of a ‘coasting’ effect with neuropathy worsening after treatment completion, highlighting different pathophysiological mechanisms between agents (Pachman et al. 2015).

Dose reduction and neuropathy outcome

Dose reduction occurred in nearly half of patients, with reduction due to neuropathy affecting more than a third of the cohort (36.2%). Paclitaxel dose reduction is common in weekly schedules
– occurring in 29% of patients in clinical trial settings (Sparano et al. 2008) and in 47% of patients in community oncology practice (Denduluri et al. 2015). A high proportion of dose reductions in weekly paclitaxel schedules are due to CIPN– necessitating dose reduction in 25%-32% of patients (Bhatnagar et al. 2014, Speck et al. 2013, Hertz et al. 2018). Importantly, though investigations into alternate preventative strategies are ongoing, dose reduction is the only current preventative strategy for CIPN recommended by the American Society of Clinical Oncology guidelines (Loprinzi et al.). While broadly, neuropathy prevalence and severity are associated with cumulative dose (Park et al. 2013), there remains little evidence concerning its effect on neuropathy outcome on an individual patient basis. In the present study, patients who experienced dose reduction demonstrated worse neuropathy at follow-up. While patients who ceased treatment after cycle 10 had comparable outcomes to those who did not discontinue treatment, patients who ceased early (cycles 6-9) had worse neuropathy outcomes despite receiving the lowest paclitaxel dose. These findings suggest that the relationship between dose reduction and neuropathy outcomes is not straightforward, and likely reflect individual neuropathy risk profiles. Patients who require early dose reductions may be more vulnerable to neuropathy and these effects may be persistent despite dose modification.

There are number of demographic and genetic characteristics which may influence neuropathy risk (Kudlowitz et al. 2013, Robertson et al. 2018, Lam et al. 2016). While many of these are known risk factors, such as older age (Barginear et al. 2019), there are many aspects of neuropathy risk that remain ill defined. These findings suggest that dose reduction alone may be insufficient to ensure favourable neuropathy outcomes. It is possible that susceptible patients develop early symptoms of neuropathy and remain worse affected regardless of dose reduction. This emphasises the need to identify risk factors that can be used to determine risk of lasting neuropathy. Interestingly, paclitaxel plasma concentration during the first treatment cycle may predict eventual dose reductions due to neuropathy (Hertz et al. 2018). This suggests that individualised dosing protocols may be able to ensure maximum benefit from chemotherapy.
while reducing side effects. However future individualised treatment protocols will need to include clinical or genetic neuropathy risk information, as dose alone is insufficient to predict neuropathy risk.

Given the use of self-report measures, it is possible that patients who are better at communicating their symptoms are more likely to receive clinical intervention and dose reduction. Documentation of neuropathy requires both clinician-based questioning and patient report and is more likely to occur when patients openly discuss neuropathy symptoms (Knoerl et al. 2019). Though clinicians may have a better understanding of the range of severity of toxicities than patients (Hertz 2019), patient report is an essential component of subjective toxicities such as CIPN. Although consensus on a ‘gold standard’ assessment is lacking (Park et al. 2013, Alberti et al. 2014, Argyriou et al. 2019), multimodal assessment of patients may assist in monitoring symptomatic patients and provide objective evidence of neurological deficits.

The current study has several strengths, including multimodal and objective assessment, prospective data collection, mid-treatment evaluation and follow-up, and a homogeneous breast cancer population receiving a uniform paclitaxel regime. However, some patients were lost to follow-up over the course of the study. Although demographic characteristics in this group did not differ, it is possible that patients experiencing more significant neuropathy had greater motivation to remain in the study. Replication in a larger cohort would allow further comparison with those who received dose reduction for other reasons, facilitating a better understanding of at-risk patients. However, it is imperative that investigation of CIPN utilises objective and comprehensive measures rather than limited or unimodal assessment often used in larger cohort or clinical trials.
Clinical implications

Weekly paclitaxel schedules are extensively used in breast cancer and CIPN is a major consideration for both patient wellbeing and treatment decisions. Previous estimates of neuropathy have varied, reflecting differences in study design, populations, treatment schedules, and CIPN assessment methods. Schedule-specific toxicity information is important to provide a guide for clinicians and patients regarding typical patterns of CIPN, especially as discrepancies between clinician and patient perceptions of CIPN have been highlighted. Clinicians should be aware that symptomatic and objective neuropathy can develop early in the treatment course and that these patients may need closer monitoring. Further, neuropathy is a long-term sequela which may be detrimental to quality of life in cancer survivors, including the risk of deficits which may require appropriate supportive services. Importantly, results suggest that dose reduction does not necessarily lead to better neuropathy outcomes, with individual risk factors playing a role. Understanding risk factors for neuropathy will be critical to determining individualized treatment strategies and improving quality of life in breast cancer survivors.
Chapter 6

Summary

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a common dose-limiting toxicity of cancer-treatment causing functional impairment and impacting quality of life. Effective prevention and treatment are lacking, and CIPN risk factors remain ill-defined. Metabolic syndrome and associated conditions have emerged as potential risk factors, due to their high prevalence and independent association with nerve dysfunction. This systematic review aimed to investigate the association between these common metabolic-lifestyle factors and CIPN. Searches were undertaken using Medline, Embase, CINAHL, Scopus, and Web of Science databases, with additional studies identified from bibliographic references cited by original and review articles. Articles that analysed metabolic-lifestyle risk factors associated with CIPN for patients treated with platinum or taxane-based chemotherapy were included.

Searches identified 6897 titles; 44 articles had full text review, with 26 studies included. Overall incidence of neuropathy ranged from 16.9% to 89.4%. Obesity had the most consistent patient-oriented evidence as a risk factor for CIPN, with moderate evidence suggesting diabetes did not increase CIPN incidence or severity. A limited number of studies supported an association with low physical activity and greater CIPN risk.

Comorbidities and lifestyle factors, particularly obesity and low physical activity may contribute to the development of CIPN. The implementation of sensitive outcome measures in large scale clinical trials are required to further elucidate CIPN risk factors and evaluate if changes in lifestyle would improve long-term CIPN outcomes for cancer survivors.

A better understanding of CIPN risk profiles may inform personalised medicine strategies and help elucidate pathophysiological mechanisms which could be targeted for neuroprotection.
**Introduction**

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a frequently encountered dose-limiting toxicity of commonly used cancer treatments (Argyriou et al. 2019). CIPN can be debilitating and irreversible, impacting long term quality of life (Swain et al. 2008, Lee et al. 2006). Effective prevention and treatment are lacking (Hershman et al. 2014), with dose modification being the only strategy to mitigate neuropathy progression. However, dose modification may attenuate treatment efficacy, potentially affecting clinical and survival outcomes (Robertson et al. 2018, Veitch et al. 2019). As such, identifying at-risk patients may assist with personalising cancer treatment and reducing neuropathy burden (Hershman et al. 2016). Though identified CIPN risk factors remain ill-defined, increasingly comorbidities and lifestyle factors have been identified as potentially contributing to an individual’s vulnerability to developing CIPN. In particular, the metabolic syndrome and associated conditions have emerged as potential risk factors, especially as they can also produce peripheral neuropathy (Greenlee et al. 2017).

Type 2 diabetes mellitus is the world’s fastest growing chronic condition (Saeedi et al. 2019), with diabetic neuropathy being the most frequent complication. As such, diabetic neuropathy is the most common cause of chronic neuropathy world-wide (Gérard 2007, Feldman et al. 2019). Similarly, the prevalence of obesity has reached pandemic levels (Blüher 2019), with 39% of adults being overweight or obese globally (WHO 2000). Though obesity is an established risk factor for type 2 diabetes (Blüher 2019), animal models have demonstrated obesity-induced microvascular injury and peripheral nerve dysfunction independent of glycaemic status (Davidson et al. 2010). Similarly, a higher prevalence of neuropathy has been reported for obese participants, even in the absence of diabetes or prediabetes (Callaghan et al. 2016b). A sedentary lifestyle is linked to increased prevalence of obesity and type-2 diabetes, with regular physical activity encouraged to prevent and mitigate both conditions and their associated complications (WHO 2000, IDF 2019).
Given the high prevalence of metabolic disorders and associated risk factors and the link of these disorders to neuropathy, it is important to clarify the relationship between metabolic factors and both CIPN incidence and severity. Therefore, this systematic review aimed to evaluate the association between these common metabolic-lifestyle factors and chemotherapy-induced neuropathy.

Methods

Search strategy and quality grading

In accordance with the PRISMA statement (Moher et al. 2010), original research articles were identified by searches of Medline, Embase, CINAHL, Scopus, and Web of Science databases in October 2019. Monthly automated searches were reviewed to ensure results were reflective of current literature up to August 2020. The search strategy (Appendix 1; Supplementary Table 1) was tailored to find articles focusing on metabolic-lifestyle risk factors associated with the incidence or severity of neuropathy due neurotoxic chemotherapies. In addition to being conducted in humans, published from 1980 and in English, searches were specified for obesity, diabetes and physical activity and limited to title, abstract or keywords fields. Initial screening was restricted to papers focusing on platinum or taxane-based cancer treatment. The strength of evidence of the summarised research was graded via the Strength of Recommendation Taxonomy (SORT) algorithm by two reviewers (HT and DM), with level A evidence being of good-quality and patient-oriented, level B comprising inconsistent or limited-quality patient-oriented evidence, and level C evidence comprising recommendation based on disease-oriented evidence, case studies, consensus, usual practice, or opinion (Ebell et al. 2004). Human studies analysing metabolic-lifestyle risk factors associated with CIPN for patients treated with platinum or taxane-based cancer treatment, satisfying level A or B evidence strength were selected for inclusion. Information was extracted from articles meeting
these criteria regarding study design, sample type and size, setting, method of CIPN assessment, overall neuropathy rate, method of measuring of obesity, diabetes and physical activity and the association with CIPN severity or incidence.

**Results**

Initially, searches identified 6897 initial articles, which was reduced to 4200 records after duplicates were removed (Fig.6.1). Additional searches of review articles were undertaken to ensure coverage, with a further 12 records being identified. Screening eliminated 4168 records resulting in 44 records which were selected for full-text review (Fig.6.1).

Twenty-six studies met criteria to be included, with a total of 21,832 participants. Most included studies were conducted in taxane-treated survivors of breast cancer (11 studies; 14164 patients; 64.9% of total), with eight studies conducted in oxaliplatin-treated colorectal cancer or esophago-gastric cancer (3910 patients; 17.9% of total) patients. Seven studies were conducted in patients with multiple cancer types treated with platinum or taxanes (3758 patients; 17.2% of total).

Effect size comparison was not possible due large variation in included patient populations, treatment type, dose and regimen, and other clinical discrepancies. Inconsistency in the measurement and definition of CIPN, and risk factors also limited pooling of the data. Moreover, CIPN was collected as a secondary measure or evaluated as a secondary analysis in many included studies.
Overall incidence of CIPN

Records identified through database searches (n=6897)

Records after duplicates removed (n=4200)

Records screened (n=4212)

Full-text articles assessed for eligibility (n=44)

Studies included in qualitative synthesis (n=26)

Additional records identified through other sources (n=12)

Records excluded (n=4168)
Exclusion criteria: Articles without a focus on metabolic and lifestyle factors and CIPN, non-human trials, paediatric population, not original research articles, abstract

Full-text articles excluded, with reasons (n=18)

7 intervention study
7 no analysis between neuropathy and risk factor
4 did not meet A/B level of evidence
Overall level of evidence for metabolic and lifestyle risk factors on CIPN incidence or severity

Moderate to good-quality and patient-oriented evidence (A/B) was most consistently available for an association between obesity and greater CIPN severity or incidence. No association between the severity or incidence CIPN and the presence of diabetes was supported by moderate level patient-oriented evidence (B). Similarly, moderate-quality evidence (B) supported an association between physical activity and better CIPN outcomes, however the number of studies supporting this association was limited (Table 6.1). It is acknowledged that there is a lack of specific randomized clinical trials focused on metabolic and lifestyle risk factors for CIPN and that the majority of evidence is from observational studies or secondary analyses.

Effect of obesity on CIPN incidence or severity

In this review, 16 studies were identified relating to CIPN and obesity (Table 6.2), with 12/16 identifying an association between obesity and greater CIPN severity or incidence and 4/16 finding no association (Table 6.1). The majority of studies (n=13) included BMI as a metric of obesity, with this being the sole marker in eight studies. Seven studies supported an association between CIPN and BMI (Barginear et al. 2019, Greenlee et al. 2017, Ghoreishi et al. 2018, Song et al. 2017, Ottaiano et al. 2016, Winters-Stone et al. 2017, Petrovchich et al. 2019), with six finding no association. However, of the six that found no association with BMI (Furlanetto et al. 2016, Schneider et al. 2012, Simon et al. 2017, Robertson et al. 2018, Dijksterhuis et al. 2019, Alejandro et al. 2013), three supported an association with another measure of obesity (BSA=2, sarcopenic obesity=1) (Dijksterhuis et al. 2019, Alejandro et al. 2013, Robertson et al. 2018). BSA was associated with CIPN severity or incidence in an additional 3 studies (Griffith et al. 2017, Hsu et al. 2019, Ghoreishi et al. 2018), with one study demonstrating no association with body weight alone (Hershman et al. 2018).
Taxanes

Nine studies examined the risk of taxane-induced neuropathy in obese breast cancer patients. Of these, five identified a link between CIPN and obesity, with four finding no association in taxane-treated patients.

In two studies using the NCI-CTCAE, obese taxane-treated patients were more likely to experience CIPN of any severity (Barginear et al. 2019, Furlanetto et al. 2016). While there was no significant link between obesity and clinician- graded CIPN in a third analysis of taxane-treated patients, the definition of CIPN was more conservative, with only those experiencing grade 2-4 being classified as having neuropathy (Schneider et al. 2012).

Three studies utilised PROMs validated for the assessment of CIPN (Greenlee et al. 2017, Hershman et al. 2018, Simon et al. 2017). Simon et al. found no associations between BMI and CIPN in women evaluated using the EORTC QLQ CIPN20 following taxane treatment (Simon et al. 2017). Similarly, pre-treatment body weight was not a significant risk factor for patient reported CIPN (FACT/GOG-Ntx13) (Hershman et al. 2018). However, in another prospective study utilising the FACT/GOG-Ntx13, obese patients demonstrated a 2-fold increased CIPN risk after 24 months compared to patients with a normal range BMI (Greenlee et al. 2017).

Obesity was associated with worse CIPN assessed using objective neurological grading (Total Neuropathy Score reduced version; TNSr© Johns Hopkins University) in two studies (Robertson et al. 2018). Worsening symptomatic and objective CIPN (increased TNSr) was significantly associated with higher BSA in breast cancer patients evaluated from the beginning of their paclitaxel treatment (Robertson et al. 2018). Similarly, Ghoresishi et al. found increased CIPN severity was associated with both higher BSA and BMI in another prospective study utilising the TNSr (Ghoresishi et al. 2018).
Song et al. defined the presence of CIPN via pharmacological prescription of pain medications (Song et al. 2017), with patients receiving treatment for CIPN being more likely to be overweight (BMI>25 kg/m²) compared to non-treated patients (Song et al. 2017).

**Oxaliplatin**

Oxaliplatin-induced neuropathy and obesity was assessed in five studies (Ottaiano et al. 2016, Dijksterhuis et al. 2019, Alejandro et al. 2013, Griffith et al. 2017, Hsu et al. 2019), with four studies conducted in colorectal cancer patients (Ottaiano et al. 2016, Alejandro et al. 2013, Griffith et al. 2017, Hsu et al. 2019) and one in advanced esophago-gastric cancer patients (Dijksterhuis et al. 2019). All five studies supported a link between increased severity or incidence of oxaliplatin-induced neuropathy and markers of obesity. Dijksterhuis et al. did not find any association between BMI and NCI-CTCAE ≥grade 2 CIPN in advanced esophago-gastric cancer patients, evaluated after three cycles of oxaliplatin (Dijksterhuis et al. 2019). However, pre-treatment sarcopenic obesity (sarcopenia + BMI >25 kg/m²), confirmed by computed tomography (CT) scans, was an independent risk factor for CIPN incidence in this study (Dijksterhuis et al. 2019). Similarly, a retrospective analysis of clinical records revealed no association between BMI and clinician documented incidence of persistent (≥14 days) CIPN, though BSA>2 was found to be an independent predictor (Alejandro et al. 2013). Conversely, prospectively collected data by Ottaiano et al., revealed a significant association between BMI and the occurrence of NCI-CTCAE ≥grade 2 CIPN up to 46 months post-oxaliplatin treatment (Ottaiano et al. 2016). However, discrepancies between these studies may be related to whether CIPN assessment took place during or post oxaliplatin treatment.

Griffith et al. evaluated oxaliplatin-induced CIPN via PROM and clinical examination. BSA was significantly higher in patients with the most severe signs and symptoms compared to those with the least deficits (Griffith et al. 2017). Similarly, Hsu et al found that higher BSA
was a significant predictor of patient reported neuropathy severity in another cohort of colorectal cancer patients (Hsu et al. 2019). However, clinical examination consisting of vibration sensibility, manual muscle testing and balance was not specifically correlated to obesity (Hsu et al. 2019).

Multiple cancer types treated with platinum or taxanes

Two studies examined the association between obesity and patient reported CIPN severity and incidence in cohorts with multiple cancer types. Amongst a cohort comprising mainly breast cancer survivors, patients reporting CIPN symptoms in the lower limbs were significantly more likely to be obese compared to asymptomatic patients (Winters-Stone et al. 2017). Similarly, Petrovchich et al. found that overweight/obese survivors reported worse pain and balance problems than those classified as normal weight (Petrovchich et al. 2019). Additionally, these patients had reduced pain sensation in lower limbs, but no other abnormalities based on quantitative sensory testing (Petrovchich et al. 2019).

Effect of diabetes on CIPN incidence or severity

Thirteen studies were identified relating to CIPN risk and diabetes (Table 6.3). Diabetic status, typically confirmed by medical records, had a reported incidence between 8.5-26%. Greater CIPN severity or incidence was associated with diabetic status in 4/13 studies, with no association being identified in 9/13 studies (Table 6.1).

Taxanes

Four studies examined the risk of taxane-induced neuropathy and diabetes (Hershman et al. 2016, Simon et al. 2017, Robertson et al. 2018, Bhatnagar et al. 2014), conducted mostly in
breast cancer patients. Of these studies, only one identified a link between and diabetes and taxane-induced neuropathy graded via NCI-CTCAE (Hershman et al. 2016).

In a large-scale analysis of clinical trial data utilising clinician-based grading (NCI-CTCAE), patients with diabetes were more likely to have CIPN following taxane treatment, with those experiencing complications from their diabetes at even greater risk (Hershman et al. 2016). However, the evaluated cohort consisted cancer patients ≥65 years old (Hershman et al. 2016), with a high incidence of diabetes with or without complications (26%), with a further 8% having confirmed complications. Though this incidence of diabetes may be consistent for this age group, with diabetes estimated to effect up to 26.8% of Americans ≥65 years old (Centers for Disease Control Prevention 2020), it may be less be less representative of some taxane-treated oncological populations. Bhatnagar et al. used recorded dose-reduction to identify patients with CIPN. In this study, diabetes was not identified as a significant risk factor for CIPN-associated dose reductions (Bhatnagar et al. 2014). However, this conservative method of identifying CIPN may not have identified all patients with CIPN. In addition, several other studies have not found any association between diabetic status and CIPN incidence. Simon et al. also found no association between diabetes and the incidence of CIPN based on validated PROMs (Simon et al. 2017). Similarly, Roberston et al. utilised patient report and objective examination to assess CIPN severity (TNSr) in comparison to baseline HbA1c levels. Abnormal HbA1c status was not associated with increased CIPN severity following taxane treatment, though only seven patients were identified with abnormal HbA1c (Robertson et al. 2018).

Oxaliplatin

Five studies evaluated diabetes in oxaliplatin-treated colorectal cancer patients (Ottaiano et al. 2016, Alejandro et al. 2013, Brown et al. 2019, Uwah et al. 2012, Ramanathan et al. 2010) using clinician-based grading to evaluate CIPN, with only one study demonstrating a
significant association between diabetes and CIPN incidence. Ottaiano, et al. found a significant association between diabetes and the incidence of NCI-CTCEA ≥grade 2 CIPN up to 46 months post-oxaliplatin treatment (Ottaiano et al. 2016), despite exclusion of those with diabetic neuropathy. However, this was not the case in a large trial evaluating CIPN 6 years post oxaliplatin treatment, with no difference in rates of ≥grade 2 CIPN being found for diabetics compared to their normoglycemic counterparts (Brown et al. 2019). Likewise, Uwah et al. found no difference in CIPN incidence or severity graded throughout oxaliplatin treatment between diabetics and non-diabetics (Uwah et al. 2012). However, diabetic patients in this study did develop CIPN at a lower cumulative dose (Uwah et al. 2012). In another large study based on pooled clinical trial data, incidence of all grade CIPN did not differ for diabetics (Ramanathan et al. 2010), but contrary to Uwah et al, this study did not find earlier onset of CIPN during oxaliplatin treatment in diabetic patients (Ramanathan et al. 2010). Persistent clinician graded CIPN was also not associated with diabetic status, however the prevalence of diabetic patients was low in this cohort (n=6) (Alejandro et al. 2013).

Multiple cancer types treated with platinum or taxanes

Four studies evaluated mixed cohorts of patients receiving platinum, taxanes or combination-based therapy (Molassiotis et al. 2019, Kus et al. 2016, Winters-Stone et al. 2017, Thomaier et al. 2020). The incidence of ≥grade 1 CIPN was significantly greater for diabetics after completing combination platinum/taxane treatment compared to non-diabetic patients (Kus et al. 2016). However, this was not the case for patients receiving taxane only treatment, with the incidence of CIPN being comparable between diabetic and non-diabetic patients (Kus et al. 2016). Similarly, Molassiotis et al found no association between diabetic status and any grade sensory-CIPN in patients receiving platinum or taxane treatment, though they highlighted a trend towards significance (\( p = 0.09 \)) (Molassiotis et al. 2019). Thomaier et al. investigated gynaecologic cancer survivors treated with neurotoxic chemotherapy. Patients reporting greater CIPN symptom severity at 6months post-treatment were more likely to have
diabetes, compared to those who reported less severe symptoms (Thomaier et al. 2020). However, in another cohort of consisting mostly of breast cancer patients, there was no difference in incidence of diabetes for those reporting lower limb CIPN symptoms compared to asymptomatic patients (Winters-Stone et al. 2017).

Effect of physical activity on CIPN incidence or severity

Five articles were identified investigating the impact of physical activity on CIPN, which mostly included breast, colorectal, ovarian and mixed cancer types (Table 6.4). One study investigated physical activity levels during treatment, three post-treatment and one across both phases. Four studies found an association between higher self-reported physical activity and lower CIPN symptoms, whilst one study found no association (Table 6.2). All studies utilised a validated CIPN PROMs. A variety of different physical activity measures were used, with three studies using physical activity guidelines to dichotomize participants as active or inactive. In the Greenlee et al. prospective cohort study, breast cancer survivors who received taxanes participating in >5 hours/week of moderate-to-vigorous intensity physical activity within 2-months of diagnosis were 44% less likely at 6 months post-treatment and 57% less likely at 24-months post-treatment to have increased CIPN symptoms (FACT/GOG-Ntx13) compared to those who participated in <2.5 hours/week (Greenlee et al. 2017). Stevinson et al. found that ovarian cancer survivors during and post-treatment (mean 73 months post-diagnosis) who met the 150-300 min/week physical activity guidelines had less CIPN symptoms (FACT/GOG-Ntx13) (Stevinson et al. 2009). However, there was no dose-response relationship between physical activity levels in excess of the guidelines and reduced CIPN symptoms (Stevinson et al. 2009). Regarding studies reporting on post-treatment physical activity levels, participants who received neurotoxic chemotherapy 6 years prior (mostly breast cancer) in the Winters-Stone et al. study who experienced CIPN symptoms reported lower total and moderate-to-vigorous
physical activity compared with those without any CIPN symptoms, as well as reduced physical function, slower gait, increased disability and increased falls risk (Winters-Stone et al. 2017). In the Mols et al. study, colorectal cancer survivors on average 5.6 years post-diagnosis who did not achieve 150 min/week of moderate-to-vigorous intensity physical activity had more severe CIPN (EORTC-QLQ-CIPN20), as well as worse quality of life across almost all domains (Mols et al. 2015). Conversely, in the Thomaier et al. prospective study, there was no difference in the proportion of gynaecological cancer survivors, mostly 1-5 years post-diagnosis, who achieved 150 min/week physical activity amongst patients with low and high CIPN symptom levels (FACT/GOG-Ntx13; 60.9% vs 59.1%) (Thomaier et al. 2020).

Discussion
CIPN displays a spectrum of symptom onset and severity, suggesting a role for individual risk factors. Identification of these risk factors may assist with personalising cancer treatment and meditating CIPN burden (Hershman et al. 2016). Accordingly, this systematic review evaluated the relationships between common metabolic-lifestyle factors and chemotherapy-induced neuropathy associated with taxane and oxaliplatin treatment. Twenty-six studies evaluating the role of metabolic-lifestyle risk factors associated with CIPN met criteria to be included. Based on these studies, obesity as a risk factor for CIPN had the most consistent patient-oriented evidence, with moderate evidence suggesting diabetes did not increase CIPN incidence or severity and only a limited number of studies evaluating the role of physical activity and CIPN outcomes.

A broad range of CIPN incidence was identified in this review (16.9-89.4%). This large variation represents heterogenous patient populations, variability in the duration of follow-up, method, and timing of the CIPN assessment, and inconsistencies in when risk factors were measured (Park et al. 2013, Rivera et al. 2017). Though the majority of studies included in this review utilised clinician-grading scales to quantify CIPN, the NCI-CTCAE is generally criticised due to a lack of inter-rater relatability and sensitivity to change (Griffith et al. 2010, Postma
et al. 1998). Patient reported outcomes were used in 7 of the reviewed studies and are
generally considered to better capture the impact of CIPN and demonstrate greater sensitivity
to change compared to clinician grading scales (Park et al. 2017a). However, inconsistencies
between the patients’ interpretation of questions and severity, and the influence of other
psychological factors may pose potential limitations (Hertz 2019, Lee et al. 2018).
Accordingly, objective techniques in addition to PROMs may provide a more thorough insight
into CIPN. Only five studies in this review included clinical examination, with only two of these
adding an objective neurophysiological measure. Similarly, objective assessment of diabetic
status and physical activity was limited, with most patients identified via medical records or
patient report. Moreover, information about the duration and persistence of these factors was
not always available. Importantly, this means that it is not always possible to examine risk
factors in the context of the natural history of CIPN progression and recovery, which may limit
the interpretation of findings. As such, evaluating CIPN risk factors and pooling data across
studies remains a challenge due to the diversity of CIPN assessment tools.

**Obesity**

In this review, good to moderate patient-centred evidence was found supporting an
association between obesity and increased severity or incidence of CIPN. An identical number
of studies supported an association in taxane, and platinum treated cohorts (n=5). However,
four studies conducted in taxane-treated patients demonstrating no association between CIPN
and obesity were also identified.

Obesity is a common comorbidity of diabetes however, in the current review many of the
studies assessing obesity and CIPN excluded patients with diabetes, suggesting a more
obesity-specific mechanism contributing to nerve dysfunction (Ghoreishi et al. 2018). Notably,
only one of the reviewed studies objectively measured HbA1c (Robertson et al. 2018) to
confirm glycaemic status, consequently individuals with unconfirmed diabetes or prediabetes
may have gone unrecognised. However, there is a growing body of evidence, including
objective assessment, which supports obesity-related neuropathy amongst normoglycemic obese individuals without cancer (Callaghan et al. 2016a, Callaghan et al. 2020b, Callaghan et al. 2016b). Specifically, normoglycemic obese participants with neuropathy had larger waist circumference measurements, compared with individuals without neuropathy, despite being comparable in BMI and other anthropometric measures. These findings suggesting that the distribution of fat may be important in mediating nerve injury (Callaghan et al. 2020b), and that central obesity more so than general obesity may be a risk factor for the development of neuropathy (Callaghan et al. 2020b). Accordingly, as BMI and to an extent BSA are metrics of generalised obesity, the lack of detailed anthropometric measurements in the studies under review may limit the ability to provide mechanistic insights into CIPN risk.

Being overweight can have deleterious effects on sensation and function in the extremities, resulting from increased mechanical force on the weight bearing joints, which may affect patient perception of symptoms (Petrovchich et al. 2019). However, amongst the 12 studies finding an association between obesity and CIPN, only 2 relied solely on patient symptom report with the remaining 10 employing other measures to define CIPN. Additionally, no association between CIPN symptoms and obesity was found in a further two studies using only PROMs, suggesting that differences in symptom perception between obese and non-obese patients may not be solely driving the differences.

Similarly, the type of metric used to classify obesity may be important in assessing toxicity risk. BMI was the most frequently utilised metric to classify obesity (n=13) mostly in taxane-treated cohorts, with 5 of these studies also including another metric of obesity (BSA=4, sarcopenic obesity=1). Consequently, amongst oxaliplatin-treated cohorts an association with CIPN and BMI was found in only one study, where BMI was the sole marker of obesity (Ottaiano et al. 2016). The remaining four studies focusing on oxaliplatin demonstrated an association with larger BSA (Alejandro et al. 2013, Hsu et al. 2019, Griffith et al. 2010) or more specific composite body measures such as sarcopenic obesity (Dijksterhuis et al. 2019). BMI is a crude
metric of body composition which may provide an inaccurate estimate muscle mass and adipose tissue (Gallagher et al. 1996, Gérard et al. 2016). Consequently, despite being correlated with BMI, BSA is employed in the oncology setting as it mitigates the variability of patient size and abnormal adiposity which can affect BMI to a greater extent (Bray et al. 2014). However, BSA is still does not comprehensively reflect body composition and may result in greater toxicity for individuals with larger BSA and unfavourable body compositions (Robertson et al. 2018, Ghoreishi et al. 2018). Specifically, reduced muscle mass and increased body fat can impact the pharmacokinetics of a large number of anti-cancer treatments depending on lipo- or hydro- solubility (Gérard et al. 2016). Paclitaxel and oxaliplatin are lipophilic agents which subsequently accumulates in adipose tissue and may be re-released (Gérard et al. 2016, Li et al. 2015). Consequently, individuals with higher body fat percentage may have longer exposure to neurotoxic agents and possibly greater CIPN risk (Dijksterhuis et al. 2019). Similarly, lower lean body mass (LBM), a more common occurrence in women, may be associated with dose limiting CIPN, as patients with low LBM relative to their BSA may effectively receive a higher dose of neurotoxic treatment (Ali et al. 2016). As such, more accurate evaluation of body composition, and subsequent normalising of dosing could assist in reducing toxicity (Ali et al. 2016).

Diabetes

Articles included in this review provided moderate patient-oriented evidence suggesting diabetes was not associated with increased CIPN incidence or severity. Diabetic peripheral neuropathy is the primary complication in patients with diabetes and the most common aetiology of neuropathy globally (Feldman et al. 2019). Consequently, many oncology trials including neurotoxic agents typically exclude patients with diabetes (Hershman et al. 2016). Five of the reviewed studies specifically excluded diabetics (Schneider et al. 2012, Hershman et al. 2018, Ghoreishi et al. 2018, Griffith et al. 2017, Hsu et al. 2019), with the majority of the remaining studies without specific analyses of diabetic patients providing no details.
surrounding the inclusion or exclusion of diabetic individuals. Amongst studies evaluating the relationship between diabetes and CIPN, only one objectively confirmed diabetic status (Robertson et al. 2018). Subsequently, the prevalence of patients with diabetes or pre-diabetes in these cohorts may be underestimated. Moreover, there is a lack of characterisation of included diabetic patients and their neuropathy status. It may be that only a subset of diabetic patients face an additional risk when exposed to neurotoxic agents, with time of diagnosis, extent of diabetic control or presence of diabetic neuropathy being more informative than status alone. Specifically, of the studies focusing on taxane treated cohorts, only one identified an increased risk of CIPN for patients with diabetes (Hershman et al. 2016). This cohort focused on an older survivor population (≥65 years) with the highest rate of diabetes of all the evaluated studies, which also included patients with diabetic complications. Though less representative of some clinical population of taxane treated patients, results may indicate that diabetes duration and complications contribute to an individual’s vulnerability for developing CIPN.

Amongst platinum treated patients, one study demonstrated a significant association between diabetes and the incidence of chronic CIPN, despite excluding diabetic neuropathy (Schmidt et al. 2000). Other reviewed studies utilising the same CIPN assessment (NCI-CTCAE), with similar rates of diabetes found no association, possibly reflecting differences in sample size and time of assessment. Though most of the reviewed studies did not support an association between diabetes and CIPN incident or severity, Uwah et al. demonstrated a difference in onset, with diabetics developing CIPN at a significantly lower cumulative dose of oxaliplatin (Uwah et al. 2012). Though this study did not specifically report the rate of dose modification, this finding may suggest that diabetics receiving oxaliplatin are more vulnerable to develop CIPN earlier in the treatment course potentially affecting treatment tolerability.
**Physical activity**

Only five studies focusing on self-reported physical activity levels as a risk factor for CIPN met criteria to be included in this review. Four studies supported the association between low physical activity and greater CIPN incidence or severity, with majority of studies displaying moderate levels of evidence. Physical activity outcomes were solely self-reported and results likely less accurate than studies using objective measures such as accelerometers (Sylvia et al. 2014). Consequently, only tentative conclusions can be drawn from the current literature, which mostly investigated post-treatment physical activity. The only study investigating physical activity during treatment found higher physical activity during treatment associated with lower CIPN severity 6- and 24-months later (Greenlee et al. 2017). Potential reasons linking higher baseline physical activity levels to reduced CIPN risk include physical activity participation protecting against physical function impairments related to CIPN (Mccrary et al. 2019a). Further, the accumulation of CIPN symptoms may reduce the ability to participate in physical activity over time and even years after treatment, which may explain the relationship we identified in three post-treatment studies (Stevinson et al. 2009, Winters-Stone et al. 2017, Mols et al. 2015). Accordingly, there is a growing body of literature investigating whether exercise interventions are beneficial for patients with CIPN, with results demonstrating improvements in both symptomatic and functional CIPN outcomes with participation (Mccrary et al. 2019a, Zimmer et al. 2018, Kleckner et al. 2018, Duregon et al. 2018). Benefits in CIPN symptoms due to increasing physical activity levels have been identified to be more prominent among older patients, with these benefits theorised to be related to exercise dose, whilst reduced chronic inflammation has been implicated as a contributing factor to the aetiology of CIPN across all age-groups (Kleckner et al. 2018, Greenlee et al. 2017). Higher physical activity levels before diagnosis, during and after treatment may facilitate improved cardio-metabolic health and reduce the likelihood of developing diabetes and obesity (Dieli-Conwright et al. 2018), potentially playing a secondary role in mediating known CIPN risk factors (Winters-Stone et al. 2017). Finally, general health benefits due to physical activity
participation including improved balance, cardiorespiratory fitness and muscle strength may contribute to improved physical function and quality of life (Kanzawa-Lee et al. 2020), both of which may be diminished with severe CIPN.

Interactions Between Metabolic and Lifestyle Risk Factors

Though some evidence exists for the independent role of obesity, diabetes and low physical activity in neuropathy risk, there exists a high degree of comorbidity. Obesity is an established risk factor for type 2 diabetes (Blüher 2019) with physical activity indicated as a mediating factor in both conditions (WHO 2020, IDF 2019). In addition to potentially contributing to the aetiology, shared mechanisms may exist which mediate CIPN development. Diabetes and obesity have both been liked to increase chronic systemic inflammation (Bertin et al. 2000, You et al. 2008). Likewise, the benefits of physical activity have been in part attributed to mitigating inflammatory processes (Gleeson et al. 2011). However, the role of inflammation in the aetiology of CIPN needs to be further elucidated. Nevertheless, there may be complex interactions between risk factors which contribute to an individual’s overall vulnerability for developing CIPN.

Conclusions

Identifying risk factors for the development and severity of CIPN is valuable for informing treatment decisions and meditating CIPN burden. Comorbidities and lifestyle factors, particularly obesity and low physical activity may contribute to an individual’s vulnerability to developing CIPN. However, the implementation of sensitive outcome measures in large scale clinical trials are required to further elucidate the patient-specific and treatment-related determinants of CIPN risk and to provide more definitive, high-level evidence (Li et al. 2020). Additionally, given the obesity pandemic and the increasing incidence of diabetes and other associated metabolic comorbidities, specific investigations are required to ascertain whether the implementation of supportive services and changes in lifestyle during or post treatment to
improve metabolic health and subsequently impact long-term CIPN outcomes for cancer survivors. Better understanding of individual risk profiles may inform personalised medicine strategies and potentially elucidate pathophysiological mechanisms which could be targeted for neuroprotection.
Table 6.1. Number of studies and overall quality of evidence supporting the association between risk factor and CIPN.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Obesity</th>
<th>Diabetes</th>
<th>Low physical activity</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Ref</td>
<td>n</td>
</tr>
<tr>
<td>Studies supporting an association</td>
<td>12</td>
<td>1,2,3,4,5,6,7,8,9,10,11,12</td>
<td>4</td>
</tr>
<tr>
<td>Studies showing no association</td>
<td>4</td>
<td>19,20,21,22</td>
<td>9</td>
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</table>

Level of Evidence

<table>
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<tr>
<th></th>
<th>A/B</th>
<th>B</th>
<th>B</th>
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Evidence was graded via the Strength of Recommendation Taxonomy (SORT) algorithm, with only studies meeting level A or B being included. Level A evidence comprised consistent and good-quality patient-oriented evidence; level B comprised inconsistent or limited-quality patient-oriented evidence.

Table 6.2. Studies evaluating obesity and CIPN.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Timing of measurement</th>
<th>Patients (n)</th>
<th>Neurotoxic agent</th>
<th>CIPN measure</th>
<th>Obesity measure</th>
<th>Overall rate of CIPN (n)</th>
<th>Rate of obesity (n)</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Taxane-based chemotherapy treatment</strong></td>
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<tr>
<td>Barginear et al. 2019</td>
<td>Prospective: Baseline-15 years</td>
<td>Long-term Follow-up</td>
<td>Breast cancer (1881)</td>
<td>Paclitaxel</td>
<td>NCI-CTCAE v4</td>
<td>Pre-treatment BMI. Obese: ≥30 kg/m²</td>
<td>65% (1226)</td>
<td>55% (1052)</td>
<td>CIPN was more likely for obese patients ( (p= .006) )</td>
</tr>
<tr>
<td>Furlanetto et al. 2016</td>
<td>Secondary analysis: Baseline-end of treatment</td>
<td>Acute post treatment</td>
<td>Breast cancer (2990)</td>
<td>Paclitaxel</td>
<td>NCI-CTCAE: Any grade</td>
<td>BMI, BSA: Medical records</td>
<td>47% (1431)</td>
<td>44.6% (248)</td>
<td>The proportion of obese patients with CIPN did not differ significantly from non-obese patients  ( (N.S) )</td>
</tr>
<tr>
<td>Schneider et al. 2012</td>
<td>Secondary analysis: Baseline- 3 weeks post treatment</td>
<td>Acute post treatment</td>
<td>Breast cancer (4554)</td>
<td>Taxanes</td>
<td>NCI-CTCAE v2. Grade 2-4</td>
<td>Pre-treatment BMI. Obese: ≥30 kg/m²</td>
<td>16.9% (770)</td>
<td>-</td>
<td>There was a non-significant trend for a higher risk of CIPN for obese patients  ( (N.S) )</td>
</tr>
<tr>
<td>Greenlee et al. 2017</td>
<td>Prospective: Baseline – 2years</td>
<td>Long-term Follow-up</td>
<td>Breast cancer (1237)</td>
<td>Taxanes</td>
<td>FACT/GOG-Ntx13</td>
<td>BMI: Medical records</td>
<td>20.4% (111)</td>
<td>34.4% (425)</td>
<td>An increased risk of CIPN was more</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Follow-up duration</td>
<td>Disease</td>
<td>Treatment</td>
<td>Prognostic Tool</td>
<td>Pre-treatment BMI and BSA</td>
<td>CIPN vs BMI</td>
<td>BMI cutoff</td>
<td>BMI criteria</td>
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<tr>
<td>Hershman et al. 2018</td>
<td>Secondary analysis: Baseline – 2 years</td>
<td>Long-term Follow-up</td>
<td>Breast cancer (218)</td>
<td>Paclitaxel</td>
<td>FACT/GOG-Nxt</td>
<td>Pre-treatment body weight</td>
<td>34.4% (69)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Simon et al. 2017</td>
<td>Cross-sectional</td>
<td>Long-term Follow-up</td>
<td>Breast cancer (126)</td>
<td>Taxanes</td>
<td>EORTC QLQ CIPN20</td>
<td>BMI: Medical records</td>
<td>73% (92)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Robertson et al. 2018</td>
<td>Prospective: Baseline-4 months post treatment</td>
<td>Mid-term Follow-up</td>
<td>Breast cancer (61)</td>
<td>Paclitaxel</td>
<td>TNSr</td>
<td>Pre-treatment BMI and BSA</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ghoreishi et al. 2018</td>
<td>Secondary analysis: Baseline – End of treatment</td>
<td>Acute post treatment</td>
<td>Breast cancer (57)</td>
<td>Paclitaxel</td>
<td>TNSr</td>
<td>BMI: Based on median ≤ 42.95 kg/m², and &gt; 42.96 kg/m². BSA.</td>
<td>42% (24)</td>
<td>BMI&gt; 42.96 kg/m²: 53% (30)</td>
<td>Increased incidence and severity associated with larger BSA (p&lt;.05.) Greater severity associated with BMI (p&lt;.05).</td>
</tr>
<tr>
<td>Song et al. 2017</td>
<td>Retrospective chart review</td>
<td>Mid-term Follow-up</td>
<td>Breast cancer (1516)</td>
<td>Taxanes</td>
<td>Prescription of pharmacological BMI: Medical Records</td>
<td>21.9% (332)</td>
<td>32.2% (107)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Obese: $\geq 30$ kg/m² likely to occur in obese ($p=.003$).
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Time Points</th>
<th>Tumor Type</th>
<th>Chemotherapy</th>
<th>CIPN Definition</th>
<th>Pre-treatment BMI</th>
<th>Follow-up BMI</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ottaiano, et al. 2016</td>
<td>Secondary analysis: Baseline- 46 months</td>
<td>Long-term Follow-up</td>
<td>Colorectal cancer (102)</td>
<td>Oxaliplatin</td>
<td>NCI-CTCAE v4. CIPN present if ≥grade 2.</td>
<td>Pre-treatment BMI</td>
<td>17.6% (18)</td>
<td>27.5% (28)</td>
</tr>
<tr>
<td>Dijksterhuis et al. 2019</td>
<td>Prospective: Cycle 1-3</td>
<td>During treatment</td>
<td>Advanced esophago-gastric cancer (88)</td>
<td>Oxaliplatin</td>
<td>NCI-CTCAE v4. Grade 2-4</td>
<td>Pre-treatment BMI. Sarcopenic obesity: sarcopenia (CT scan) and BMI &gt;25 kg/m²</td>
<td>20.5% (18)</td>
<td>19.7% (17)</td>
</tr>
<tr>
<td>Alejandro et al. 2019</td>
<td>Retrospective chart review</td>
<td>During treatment</td>
<td>Colorectal cancer (50)</td>
<td>Oxaliplatin</td>
<td>Clinician documented CIPN persisting &gt;14 days</td>
<td>BSA, BMI, body weight: Medical records</td>
<td>48% (24)</td>
<td>BSA&gt;2: 29% (20)</td>
</tr>
<tr>
<td>Study</td>
<td>Study Details</td>
<td>Interventions</td>
<td>Outcomes</td>
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<tr>
<td>Griffith et al. 2017</td>
<td>Secondary analysis: Baseline – End of</td>
<td>Acute post treatment</td>
<td>Colorectal cancer (148) Oxaliplatin TNSc BSA: Medical records 63% (94)</td>
<td></td>
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<tr>
<td></td>
<td>treatment</td>
<td></td>
<td>Higher BSA in patients with severe CIPN compared to those with least deficits (p&lt;.05). A/B</td>
<td></td>
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<tr>
<td>Hsu et al. 2019</td>
<td>Prospective: Baseline- End of treatment</td>
<td>Acute post treatment</td>
<td>Colorectal cancer (77) Oxaliplatin Clinician grading, patient report, and clinical examination BSA: Medical records 89.4% (69) - Higher BSA was significant predictor of patient reported CIPN severity (p&lt;.0001). No analysis for clinical examination. B</td>
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</table>

**Mixed Platinum and Taxane based chemotherapy treatment**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Details</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winters-Stone et al. 2017</td>
<td>Secondary data analysis: cross-sectional</td>
<td>Long-term Follow-up</td>
<td>Mostly Breast cancer (512) Unknown* FACT/GOG-Ntx13 (lower limb symptoms) BSA: Patient-report 47% (240) - Patients reporting symptoms were more likely to be obese (p&lt;.05). B</td>
</tr>
<tr>
<td>Petrovchich et al. 201</td>
<td>Cross-sectional</td>
<td>Mid-term Follow-up</td>
<td>Various cancer types with CIPN (416) Platinum and Taxanes Patient reported pain and balance; QST# BMI: Patient-report - 22.1% (92) Overweight/obese survivors had reduced pain sensation in lower limbs and reported worse A/B</td>
</tr>
</tbody>
</table>
pain and balance problems (p<.05).


Unless otherwise specified, all studies considered the following BMI classifications: Normal: <25 kg/m², Overweight: ≥25 kg/m², Obese: ≥30 kg/m². *Studies with unknown neurotoxic agents were included based on the cancer population likely receiving platinum or Taxane treatment. Acute post treatment: up to 1-month cessation of neurotoxic cancer treatment. Mid-term Follow-up: 2 months-12months post cessation of neurotoxic cancer treatment. Long term Follow-up: ≥2 years post cessation of neurotoxic cancer treatment.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Timing of measurement</th>
<th>Patients (n)</th>
<th>Neurotoxic agent</th>
<th>CIPN measure</th>
<th>Diabetes Measure</th>
<th>Overall rate of CIPN (n)</th>
<th>Rate of Diabetes (n)</th>
<th>Summary of findings</th>
<th>SORT Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hershman et al. 2018</td>
<td>Retrospective chart review</td>
<td>During treatment</td>
<td>Multiple cancer types ≥65 years old (1401)</td>
<td>Taxanes</td>
<td>NCI-CTCAE v2 ≥grade 2.</td>
<td>Medical records</td>
<td>18% (251)</td>
<td>22-26% (364)</td>
<td>Patients with any diabetes more likely to have CIPN. (p =.001). With greater risk for those with diabetic complications (p&lt;.002)</td>
<td>B</td>
</tr>
<tr>
<td>Simon et al. 2017</td>
<td>Cross-sectional</td>
<td>Long-term Follow-up</td>
<td>Breast cancer (126)</td>
<td>Taxanes</td>
<td>EORTC QLQ CIPN20</td>
<td>Medical records</td>
<td>73% (92)</td>
<td>19.8% (25)</td>
<td>No associations between presence of diabetes and CIPN incidence (N.S).</td>
<td>B</td>
</tr>
<tr>
<td>Robertson et al. 2018</td>
<td>Prospective: Baseline-4</td>
<td>Mid-term Follow-up</td>
<td>Breast cancer (61)</td>
<td>Paclitaxel</td>
<td>TNSr</td>
<td>Pre-treatment</td>
<td>-</td>
<td>11.5% (7)</td>
<td>Abnormal HgbA1c was not a</td>
<td></td>
</tr>
</tbody>
</table>

Table 6.3. Studies evaluating diabetes and CIPN
<table>
<thead>
<tr>
<th>Study: Bhatnagar et al. 2014</th>
<th>Retrospective chart review</th>
<th>During neurotoxic treatment</th>
<th>Breast cancer (123)</th>
<th>Taxanes</th>
<th>Dose reductions for CIPN</th>
<th>Medical records</th>
<th>HbA1c analysis</th>
<th>significant risk factor (N.S.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study: Ottaiano, et al. 2016</td>
<td>Secondary analysis: Baseline- 46 months</td>
<td>Long term Follow-up</td>
<td>Colorectal cancer (102)</td>
<td>Oxaliplatin</td>
<td>NCI-CTCAE. ≥grade 2</td>
<td>Medical records</td>
<td>Patients with diabetic neuropathy were excluded</td>
<td>17.6% (18)</td>
</tr>
<tr>
<td>Study: Brown et al. 2019</td>
<td>Secondary analysis: Baseline- 6 years</td>
<td>Long-term Follow-up</td>
<td>Colorectal cancer (1796)</td>
<td>Oxaliplatin</td>
<td>NCI-CTCAE. ≥grade 2</td>
<td>Medical records</td>
<td>36% (653)</td>
<td>15% (268)</td>
</tr>
<tr>
<td>Study: Uwah et al. 2012</td>
<td>Retrospective chart review</td>
<td>During treatment</td>
<td>Colorectal cancer (62)</td>
<td>Oxaliplatin</td>
<td>NCI-CTCAE. ≥grade 2</td>
<td>Medical records</td>
<td>24% (15)</td>
<td>24% (15)</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Type</td>
<td>Time Period</td>
<td>Tumor Type</td>
<td>Chemotherapy</td>
<td>Neurotoxicity Scale</td>
<td>Data Source</td>
<td>Incidence</td>
<td>Incidence of All Grade CIPN</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>Ramanathan et al. 2009</td>
<td>Secondary analysis: Baseline-End of treatment</td>
<td>Acute post treatment</td>
<td>Colorectal cancer (1587)</td>
<td>Oxaliplatin</td>
<td>NCI-CTCAE; Oxaliplatin-specific neurotoxicity scale</td>
<td>Medical records</td>
<td>86.8% (1372)</td>
<td>8.5% (135)</td>
</tr>
<tr>
<td>Alejandro et al. 2013</td>
<td>Retrospective chart review</td>
<td>During treatment</td>
<td>Colorectal cancer (50)</td>
<td>Oxaliplatin</td>
<td>Clinician documented CIPN persisting &gt;14 days</td>
<td>Medical records</td>
<td>48% (24)</td>
<td>12% (6)</td>
</tr>
<tr>
<td>Molassiotis et al. 2011</td>
<td>Secondary analysis: cross-sectional</td>
<td>Mid-term Follow-up</td>
<td>Multiple cancer types (255)</td>
<td>Platinum and Taxanes</td>
<td>NCI-CTCAE</td>
<td>Medical records</td>
<td>12.9 (33)</td>
<td>14.5% (37)</td>
</tr>
<tr>
<td>Kus et al. 2016</td>
<td>Secondary analysis: Baseline-End of treatment</td>
<td>Acute post treatment</td>
<td>Multiple cancer types (374)</td>
<td>Taxanes or Taxane platinum combination</td>
<td>NCI-CTCAE ≥grade 1</td>
<td>Medical records</td>
<td>Taxane only: 47% (127) Combination: 62.5% (65)</td>
<td>21% (81)</td>
</tr>
<tr>
<td>Study</td>
<td>Analysis Type</td>
<td>Follow-up Time</td>
<td>Cancer Type</td>
<td>Neurotoxicity Score</td>
<td>Comparison Method</td>
<td>Incidence</td>
<td>Difference</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Winters-Stone et al. 2017</td>
<td>Secondary data analysis: cross-sectional</td>
<td>Long-term Follow-up</td>
<td>Mostly breast cancer (512)</td>
<td>Unknown</td>
<td>FACT/GOG-Ntx13 (lower limb symptoms)</td>
<td>Self-report via the Charlson comorbidity index</td>
<td>47% (240)</td>
<td>11% (57)</td>
</tr>
<tr>
<td>Thomaier et al. 2020</td>
<td>Secondary analysis: Baseline- 6 months</td>
<td>Mid-term Follow-up</td>
<td>Gynaecologic cancer (194)</td>
<td>Unknown</td>
<td>FACT/GOG-Ntx13 (&lt;11 v ≥11points)</td>
<td>Patient report</td>
<td>Greater severity: 34% (66)</td>
<td>11.6% (22)</td>
</tr>
</tbody>
</table>

EORTC QLQ CIPN20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT/GOG-Ntx13: Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity questionnaire; OR: Odds ratio; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events TNSr: Total Neuropathy Score reduced version- A validated composite grading measure, comprising, clinical examination, patient symptom report and nerve conduction studies; *Studies with unknown neurotoxic agents were included based on the cancer population likely receiving platinum or Taxane treatment. Acute post treatment: up to 1-month cessation of neurotoxic cancer treatment. Mid-term Follow-up: 2 months-12months post cessation of neurotoxic cancer treatment. Long term Follow-up: ≥2 years post cessation of neurotoxic cancer treatment.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Timing of measurement</th>
<th>Patients (n)</th>
<th>Neurotoxic agent</th>
<th>CIPN measure</th>
<th>Physical activity measure</th>
<th>Overall rate of CIPN (n)</th>
<th>Physical activity levels</th>
<th>Summary of findings</th>
<th>SORT Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenlee et al. 2017</td>
<td>Prospective: Baseline, 6 months and 2 years</td>
<td>Long-term Follow-up</td>
<td>Breast cancer (1237)</td>
<td>Taxanes</td>
<td>FACT/GOG -Ntx13</td>
<td>Arizona Activity Frequency Questionnaire</td>
<td>20.4% (111)</td>
<td>70.1% achieved PA guidelines within 2-months post-diagnosis.</td>
<td>High MVPA within 2-months post-diagnosis has 44% and 57% less likelihood to have increased CIPN at 6-month (p=.03) and 24-month (p=.02) follow-up.</td>
<td>A</td>
</tr>
<tr>
<td>Stevinson et al. 2009</td>
<td>Cross-sectional</td>
<td>On and off treatment</td>
<td>Ovarian cancer (359)</td>
<td>Unknown*</td>
<td>FACT/GOG -Ntx13</td>
<td>Godin Leisure Time Exercise Questionnaire</td>
<td>-</td>
<td>31.1% achieved PA guidelines^ Mean=99±161 min/week of MVPA</td>
<td>Meeting PA guidelines^ on average 6.1-years post-diagnosis (9% receiving treatment)</td>
<td>B</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Study Design</td>
<td>Tumor Type</td>
<td>Lesion Type</td>
<td>Neurological Assessment</td>
<td>MVPA Baseline (kcal/day)</td>
<td>MVPA Post-treatment (kcal/day)</td>
<td>Energy Expenditure Associated with CIPN (kcal/day)</td>
<td>Notes</td>
<td></td>
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</tr>
<tr>
<td>Winters-Stone et al. 2017</td>
<td>Secondary analysis: Cross-sectional</td>
<td>Long-term Follow-up</td>
<td>Mostly breast cancer (512)</td>
<td>Unknown*</td>
<td>Patients classified as having CIPN based on presence of lower limb symptoms from FACT/GOG-Ntx13</td>
<td>Community Healthy Activities Model Program for Seniors Questionnaire</td>
<td>47% (240)</td>
<td>$171 \pm 204$ kcal/day of MVPA</td>
<td>Reduced MVPA and total PA energy expenditure (kcal/day) in those with CIPN symptoms ($p&lt;.01$) on average 6-years post-treatment.</td>
<td>B</td>
</tr>
<tr>
<td>Mols et al 2015</td>
<td>Cross-sectional</td>
<td>Long-term Follow-up</td>
<td>Colorectal cancer (1648)</td>
<td>Unknown*</td>
<td>EORTC QLQ-CIPN20</td>
<td>European Prospective Investigation into Cancer Physical Activity Questionnaire</td>
<td>-</td>
<td>93% of chemotherapy treated patients achieved PA guidelines Mean=$12.2 \pm 8.8$ hours/week of MVPA.</td>
<td>Not meeting PA guidelines on average 5.6-years post-diagnosis associated</td>
<td>B</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Follow-up</td>
<td>Disease</td>
<td>CIPN</td>
<td>Measure</td>
<td>Gait Speed</td>
<td>Outcome</td>
<td>Conclusion</td>
<td></td>
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</tr>
<tr>
<td>Thomaier et al 2020</td>
<td>Prospective: Baseline and 6 months</td>
<td>Mid-term Follow-up</td>
<td>Gynaecological cancer (194)</td>
<td>Unknown*</td>
<td>FACT/GOG -Ntx 13 (&lt;11 v ≥11 points)</td>
<td>Patient report: min/week of MVPA</td>
<td>Gait severity: 34% (66)</td>
<td>60% achieved PA guidelines</td>
<td>No difference in the proportion of participants meeting PA guidelines^ (mostly 1 to 5 years post-diagnosis) between those with low and high CIPN symptoms (N.S).</td>
<td></td>
</tr>
</tbody>
</table>

EORTC-QLQ-CIPN20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT/GOG-Ntx 13: Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity questionnaire; OR: Odds ratio; CI: Confidence interval; PA: Physical activity; MVPA: Moderate-vigorous physical activity. ^150 min/week MVPA *Studies with unknown neurotoxic agents were included based on the cancer population likely receiving platinum or taxane treatment. Acute post treatment: up to 1-month cessation of neurotoxic cancer treatment. Mid-term Follow-up: 2 months-12 months post cessation of neurotoxic cancer treatment. Long term Follow-up: ≥2 years post cessation of neurotoxic cancer treatment.
Chapter 7

The Impact of Obesity on Neuropathy

Outcomes for Paclitaxel and Oxaliplatin-

-treated Cancer Survivors
Summary

Chemotherapy-induced peripheral neuropathy (CIPN) is a major side effect of neurotoxic cancer treatment, often impacting treatment tolerability and patient functioning. Factors predicting an individual’s vulnerability for developing CIPN remain ill-defined. However patient characteristics may contribute to CIPN risk, with obesity being a prevalent patient comorbidity. This study aimed to evaluate if being overweight (BMI≥25kg/m²) was associated with worse symptomatic, clinical, and functional CIPN following neurotoxic cancer treatment.

379 cancer survivors were assessed 5 (IQR:3-5) months post oxaliplatin or paclitaxel treatment via comprehensive patient reported, clinical and functional CIPN measures. Patients classified as overweight (BMI≥25kg/m²) were compared to those within the normal BMI range (< 25 kg/m²). Multilinear regression was conducted to evaluate the association between patient clinical factors and CIPN severity.

Most patients reported CIPN symptoms (78%), with deficits evident on clinical examination. Overweight patients (n=242, 63.8%) had significantly worse CIPN across symptomatic, objective clinical and functional outcomes compared to those with a normal BMI (p<.05). In multivariate linear regression, older age (β=.088, 95%CI=.053-.122, p<.001), larger waist circumference (β=.030, 95%CI=.001-.059, p<.05), and larger BSA (β=2.41, 95%CI=.340-4.48, p<.05) were associated with CIPN. Diabetes and BMI were significant on univariate analysis but not in the final models.

Overweight patients represent a large proportion of cancer survivors who may be particularly impacted by CIPN, requiring closer monitoring and referral to supportive services. Accessible data such as a patient’s general and abdominal obesity status may aid in formulating personalised treatment. Identifying routinely measured patient characteristics which may contribute to an individual’s CIPN risk profile could assist with informing treatment decisions.
Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting side effect of neurotoxic cancer treatments including oxaliplatin and paclitaxel which are routinely used to treat common cancers (Argyriou et al. 2019). CIPN can be irreversible, causing functional impairment and detriment to long-term quality of life (Swain et al. 2008). Despite the prevalence and persistent impact of CIPN, there is a paucity of effective prevention and treatment (Hershman et al. 2014). Dose modification is currently the only recommended strategy available to clinicians to mitigate CIPN (Loprinzi et al.). However, dose modification may reduce treatment efficacy (Robertson et al. 2018, Veitch et al. 2019) and the impact of dose modification on long term CIPN outcomes remain poorly characterised. Additionally, a spectrum of CIPN onset and severity can occur amongst homogenously treated cohorts, suggesting a role for individual risk factors (Hershman et al. 2016). However, risk factors which contribute to an individual's vulnerability to develop CIPN remain ill-defined, in part due to the lack of a comprehensive quantitative CIPN assessment to validate putative risk factors (Rivera et al. 2017). Regardless, patient characteristics, comorbidities and lifestyles have been increasingly indicated as potential risk factors. In particular, conditions associated with metabolic syndrome have emerged as probable candidates, due to their association with type 2 diabetes mellitus, a known aetiology of peripheral neuropathy (Greenlee et al. 2017).

Of the conditions associated with metabolic syndrome obesity is the most prevalent, reaching pandemic levels (Blüher 2019) with 39% of adults being overweight or obese worldwide (WHO 2020). Although obesity is a frequent comorbidity of type 2 diabetes (Blüher 2019), evidence from animal models and patient studies have suggested that obesity may induce peripheral nerve dysfunction in normoglycemic conditions (Callaghan et al. 2016b, Davidson et al. 2010). Further, centralised fat distribution has been specifically identified as contributing to greater neuropathy risk in non-oncological populations (Davidson et al. 2010, Callaghan et al.)
2020b, Callaghan et al. 2016b), possibly indicating neurotoxic effects associated with obesity.

A recent systematic review evaluating CIPN risk factors in taxane and oxaliplatin treated patients, highlighted the discord around the role of obesity, mostly defined using body mass index (BMI), in the development of CIPN (Timmins et al. 2021). Though some studies demonstrated an association between obesity and greater CIPN prevalence and severity (Barginear et al. 2019, Ottaiano et al. 2016, Dijksterhuis et al. 2019), other investigations failed to find any association (Furlanetto et al. 2016, Schneider et al. 2012, Hershman et al. 2018, Simon et al. 2017). These discrepancies likely reflect heterogeneity in patient populations, timing of assessment and definitions of CIPN. Moreover, though no standard CIPN measure was utilised across all studies, patients were commonly assessed using clinician grading scales (Barginear et al. 2019, Ottaiano et al. 2016, Dijksterhuis et al. 2019) which display poor sensitivity, and lack of concurrence with patient reports and objective CIPN measures (Postma et al. 2005b, Basch et al. 2006).

Further, though CIPN can result in functional impairment, investigations into the additional impact obesity may have on patient function is lacking. As such the association between obesity and CIPN outcomes remains ill defined.

Given the prevalence of obesity, it is important to clarify the impact being overweight may have on CIPN outcomes. Therefore, this study aimed to evaluate if being overweight was associated with worse symptomatic, clinical and functional CIPN outcomes following treatment with two of the most commonly utilised neurotoxic chemotherapies, oxaliplatin and paclitaxel.
Methods

Patients and study design

Patients who received oxaliplatin or paclitaxel treatment were referred from July 2015 to February 2020 for comprehensive cross-sectional clinical and functional assessments 3-12 months post completion of neurotoxic treatment. Patients were eligible for inclusion if they were still receiving non-neurotoxic cancer treatment such as trastuzumab or 5-fluorouracil at the time of assessment. Written informed consent was obtained in accordance with the Declaration of Helsinki, with studies approved by the Sydney Local Health District and South Eastern Sydney Local Health District Human Research Ethics Committees.

Neuropathy Assessment

Patients reported symptomatic CIPN burden via the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx13, range: 0-52), (Calhoun et al. 2003, Webster et al. 2003), with lower scores indicating greater burden. Items 1 ‘I have numbness or tingling in my hands’ and 2: ‘I have numbness or tingling in my feet’ were used to describe specific patient reported symptoms and severity (Timmins et al. 2020a).

CIPN was clinically assessed via the Total Neuropathy Score clinical version (TNSc © Johns Hopkins University), a composite grading score of patient symptom report and clinical neurological examination, which addresses some of the limitations of unimodal CIPN assessment (Cavaletti et al. 2006, Comblath et al. 1999, Argyriou et al. 2019), with greater CIPN severity indicated by higher scores (range 0-24) (Cavaletti et al. 2006, Comblath et al. 1999). Von Frey monofilaments and two-point discrimination were preformed to assess distal sensation in the upper and lower limbs respectively. Similarly, functional assessments were undertaken using the grooved pegboard test as a measure of upper limb manual dexterity (Schmidt et al. 2000). Lower limb functioning, indicated by standing balance was assessed via postural sway using a Swaymeter (Neuroscience Research Australia, Sydney). (Mccrary et al.
Balance conditions were combined into a summed postural sway path length, with longer length indicating greater deficits (Mccrary et al. 2019b).

**Clinical information and body composition measurements**

Clinical and treatment information was retrieved from medical records in addition to pre-treatment height (m) and weight (kg). Body mass index (BMI) was calculated using weight (kg) divided by height (m) squared. Patients were classified as normal weight (BMI: <25 kg/m²) or overweight (BMI: ≥25kg/m²) (WHO 2020). Normal body surface area (BSA) was classified ≤1.9 m² for males and ≤1.6 m² for females calculated via the Mosteller equation (Mosteller 1987). Chemotherapy dose was prescribed based on uncapped BSA. Dosing information was used to calculate relative dose intensity (RDI, %) by dividing the total dose of administered chemotherapy treatment by planned total dose originally (Wildiers et al. 2011). Metastatic cases were managed according to Australian government cancer treatment protocol guidelines, supplemented by clinician notes (Cancer Institute NSW 2020).

During CIPN assessments additional anthropometric measurements were taken in a subset of patients (n=149). Hip measurements (cm) were taken from the largest part of the buttocks, with waist measurements (cm) taken in line with the navel (Callaghan et al. 2016b). Abdominal obesity was defined as elevated waist circumference (males: ≥94 cm, females: ≥80 cm) based on published consensus guidelines (Alberti et al. 2009). Further measures for abdominal obesity were defined by the waist-to-hip ratio (WHR), calculated as waist circumference divided by hip circumference (males: ≥0.95, females: ≥0.80) (WHO 2000).


**Data analysis**

Chi square or independent samples t-test were used to compare categorical or continuous clinical factors and CIPN outcomes between oxaliplatin and paclitaxel-treated patients. Additionally, CIPN outcomes were compared between patients classified as normal or overweight based on BMI. Overweight patients (BMI between 25-29 kg/m²) and obese patients (BMI≥30 kg/m²) were combined and compared to patients within the normal BMI range. Bootstrapping was performed based on 1000 bootstrap samples. Results are presented as the mean with standard deviation or median with inter quartile range (IQR) as appropriate.

Linear regression was utilised to assess the association between measurements of obesity (BMI, BSA (uncapped), waist circumference and waists-to-hip ratio) and clinical factors (age, sex, diabetic status, time since treatment, cumulative dose, relative dose intensity) with CIPN severity based on the TNSc. Missing data was handled using listwise deletion with results indicating complete case analysis. Variables identified as significant ($p<.05$) in univariate analysis were included in multivariate models. Factors not contributing to the model ($p>.1$) were eliminated during backward stepwise regression, with the remaining significant variables retained in the final multivariable model being reported. To avoid violating collinearity, two models were constructed substituting generalized measures of obesity (BSA and BMI) (Callaghan et al. 2020b). Q-Q residual plots were used to check normality and variance of the data. All analyses were performed using SPSS (Version 25, IBM) with significance indicated as $p<.05$. 
Results

Patient characteristics

The cohort consisted of 379 patients (age: 57.9±12.5 years, female: 77.8%, n=295) who had completed neurotoxic cancer treatment 5 (IQR: 3-8) months previously (Table 7.1.). The most common cancer types were breast (40.6%), colorectal (27.7%) and ovarian (12.9%). Paclitaxel (n=245) and oxaliplatin-treated participants (n=134) were comparable in age and diabetic status, but differed significantly in time since treatment completion, relative dose intensity and sex, with more paclitaxel-treated patients being female, receiving a higher dose intensity and assessed at a longer time since treatment completion (p<.05; Appendix:2 Supplementary Table 1.).
## Table 7.1. Patient characteristics

<table>
<thead>
<tr>
<th>Demographic and clinical data</th>
</tr>
</thead>
</table>

### Age (years)

| Mean ± SD (Range) | 57.9 ± 12.47 (28 – 87) |

### Sex, Female (n, %)

| 295 (77.8) |

### Diabetes (n, %)

| 34 (9.2) |

### Cancer type (n, %)

| Breast | 154 (40.6) |
| Colorectal | 105 (27.7) |
| Ovarian | 49 (12.9) |
| Endometrial | 34 (9.0) |
| Upper Gastrointestinal | 19 (5.0) |
| Pancreatic | 15 (4.0) |
| Cervical | 3 (0.8) |

### Cancer stage (n, %)

| I | 27 (7.1) |
| II | 105 (27.7) |
| III | 144 (38.0) |
| IV | 80 (21.1) |
| Unknown | 23 (6.1) |

### Time since treatment (months)

| Median (IQR) | 5 (3-8) |

### Relative dose intensity (%)

| Mean ± SD (Range) | 86.86 ± 13.16 (50-100) |

### Cumulative dose (mg/m²) ^

<table>
<thead>
<tr>
<th>Mean ± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Oxaliplatin</td>
</tr>
</tbody>
</table>

^ Cumulative dose based on uncapped BSA
Of the total cohort, 63.8% (n=242) were overweight (BMI: ≥25kg/m$^2$), with 45.5% (n=110) of these overweight patients having a BMI ≥30kg/m$^2$. Based on sex-specific values, 79.3% (n=298) had abnormal BSA. Of those with measures of central obesity (n=149), 85.2% (n=127) had abnormal waist circumference and waist to hip ratio (WHR) (Table 7.2.). There was no difference in the proportion of patients with abnormal waist circumference, BMI or BSA between oxaliplatin and paclitaxel-treated groups (N.S, Appendix 2: Supplementary Table 1), with the proportion of oxaliplatin and paclitaxel treated patients being comparable in the overweight (BMI: ≥25kg/m$^2$) and normal weight groups.

**Table 7.2.** Mean (±SD) anthropometric measures for males and females with the total number of abnormal cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Total abnormal cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1.38-1.87</td>
<td>1.46-1.81</td>
<td>--</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>82.14±14.81</td>
<td>72.63±16.93</td>
<td>--</td>
</tr>
<tr>
<td>Range</td>
<td>47.00-125.00</td>
<td>42.9-140.00</td>
<td>--</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td>26.7±4.49</td>
<td>27.45±6.48</td>
<td>63.8</td>
</tr>
<tr>
<td>(kg/m²)</td>
<td>19-38</td>
<td>16-51^-</td>
<td>242</td>
</tr>
<tr>
<td><strong>Body Surface Area</strong></td>
<td>1.99±.20</td>
<td>1.8±.21</td>
<td>79.3</td>
</tr>
<tr>
<td>(m²)^A</td>
<td>1.43-2.52</td>
<td>1.34-2.54</td>
<td>298</td>
</tr>
<tr>
<td><strong>Waist circumference</strong></td>
<td>100.02±10.05</td>
<td>96.7±15.74</td>
<td>85.2</td>
</tr>
<tr>
<td>(cm)</td>
<td>79-117</td>
<td>67-150</td>
<td>127</td>
</tr>
<tr>
<td><strong>Hip circumference</strong></td>
<td>102.63±9.81</td>
<td>104.86±16.11</td>
<td>--</td>
</tr>
<tr>
<td>(cm)</td>
<td>82.50-118</td>
<td>68-164</td>
<td>--</td>
</tr>
<tr>
<td><strong>Waist to hip ratio</strong></td>
<td>.98±.08</td>
<td>.93±.15</td>
<td>85.2</td>
</tr>
<tr>
<td>Range</td>
<td>.84-1.17</td>
<td>.52-1.39</td>
<td>127</td>
</tr>
</tbody>
</table>

^BSA not capped at 2m²
Symptomatic, clinical and functional CIPN severity

Clinical, functional and patient-reported neurological assessment outcomes for the whole cohort are presented in Table 7.3. Oxaliplatin-treated patients demonstrated greater CIPN severity compared to paclitaxel-treated patients, across patient reported, clinical and functional outcomes, suggesting greater symptomatic and objective CIPN in this cohort (Appendix 2: Supplementary Table 7.2).

In total, CIPN symptoms were reported by the majority of the total cohort (78.5%, n=296), with mild to moderate severity on patient reported and clinical outcome measures (Table 7.3) in line with previous reports (Park et al. 2011b, Timmins et al. 2020b). More patients reported persistent numbness and tingling in the feet (74.5%; n=281) compared to the hands (66%; n=250).

During clinical examination reduced deep tendon reflexes (64.8%, n=239) and deficits in pinprick sensibility (61.5%, n=227) were most frequently observed, with vibration sensibility being reduced in 34.1% of patients (n=126). Manual muscle testing was normal for most patients (91.6%, n=338), consistent with a sensory predominant neuropathy.

CIPN outcomes for patients classified as overweight

Overweight patients (BMI: ≥25kg/m²) had greater overall patient reported symptom burden compared to patients classified as normal weight (FACT/GOG-Ntx13; normal weight:43.80±8.35, overweight: 40.20±8.93, p<.01, Table 7.3.) Specifically, overweight patients were more likely to report symptoms of numbness and tingling in the hands ($X^2(1, N=375) =14.33, p<.001$) and feet ($X^2(1, N= 375) =16.60, p<.001$, Fig. 7.1), with a significantly larger proportion also reporting greater severity of CIPN symptoms in the feet compared to patients with normal weight ($X^2(1, N=375) =5.04, p<.05$, Fig. 7.1).
Table 7.3. Mean (±SD) CIPN outcomes for the total cohort, normal, overweight patients based on BMI.

<table>
<thead>
<tr>
<th>Patient symptom report</th>
<th>Total cohort n=379</th>
<th>BMI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal (n= 135) mean± SD</td>
<td>Overweight (n=242) mean± SD</td>
</tr>
<tr>
<td>FACT/GOG-Ntx13</td>
<td>41.58±8.86</td>
<td>43.80±8.35</td>
<td>40.20±8.93</td>
</tr>
<tr>
<td>Range</td>
<td>16-52</td>
<td>18-52</td>
<td>16-52</td>
</tr>
<tr>
<td>Clinical and sensory assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNSc</td>
<td>4.41±2.90</td>
<td>3.71±2.85</td>
<td>4.85±2.86</td>
</tr>
<tr>
<td>Range</td>
<td>0-14</td>
<td>0-14</td>
<td>0-14</td>
</tr>
<tr>
<td>Upper limb sensory discrimination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Von frey monofilament detection threshold (mN)</td>
<td>1.75±6.61</td>
<td>1.49±7.98</td>
<td>1.93±5.59</td>
</tr>
<tr>
<td>Range</td>
<td>.12-90.51</td>
<td>.12-90.51</td>
<td>.12-51.98</td>
</tr>
</tbody>
</table>
Normal body mass index (BMI): < 25 kg/m²; * = p<.05, comparison between normal and overweight patients. Bootstrapping was conducted based on 1000 bootstrapped samples. Body mass index (BMI; n=377) Normal: < 25 kg/m²; Overweight: ≥25 kg/m².

<table>
<thead>
<tr>
<th>Lower limb sensory discrimination</th>
<th>12.03±3.85</th>
<th>11.99±3.76</th>
<th>12.03±3.90</th>
<th>.933</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-point discrimination threshold (mm)</td>
<td>2-15</td>
<td>4-15</td>
<td>2-15</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upper limb functional assessment</th>
<th>77.84±25.45</th>
<th>72.75±24.43</th>
<th>80.94±25.72</th>
<th>.010*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegboard (Sec)</td>
<td>40.06-208.32</td>
<td>42.73-173.30</td>
<td>40.06-208.32</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Balance assessment</th>
<th>778.92±265.51</th>
<th>723.47±235.79</th>
<th>824.26±281.89</th>
<th>.009*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural sway path length (mm)</td>
<td>232-1683</td>
<td>232-1306</td>
<td>358-1683</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 7.1. The percentage of overweight (BMI ≥25kg/m²) and normal weight patients reporting CIPN symptoms and functional impairment in the hands and feet based on items from the FACT/GOG-Ntx13, * = p<.05.
Compared to those with normal weight, overweight individuals (BMI: ≥ 25 kg/m²) demonstrated significantly worse deficits on clinical examination (TNS; normal weight: 3.71 ± 2.85, overweight: 4.85 ± 2.86, p < .05). Moreover, though they did not differ in specific tests of distal sensation, consistent with patient report, overweight individuals were more likely to demonstrate functional deficits in the upper limbs (peg board; normal weight: 72.75 ± 24.43 sec, overweight: 80.93 ± 25.72 sec, p < .05) as well as significantly greater balance deficits (postural sway; normal: 723.48 ± 235.79 mm, overweight: 824.26 ± 281.88 mm, p < .01; Table 7.3).

**Association between clinical factors, generalised and centralised obesity measures and CIPN**

Linear regression was conducted to evaluate the association between patient and clinical variables, including measures of general and central obesity, with CIPN severity (TNSc).

Univariate obesity measures and clinical variables associated with CIPN are presented in Table 7.4. WHR, cumulative dose, relative dose intensity and months post-treatment were non-significant factors in univariate analysis and not included in multivariate models (N.S.).

Two multivariable models were constructed based on each measurement of generalised obesity (Model 1: BMI, Model 2: BSA). In the first multivariate model (F (2, 134) = 15.91, p < .001, r² = .19), older age (B = .088, 95% CI = -1.22, p < .001) and larger waist circumference (B = .030, 95% CI = .001 - .059, p < .01) were significantly associated with worse CIPN severity. However, BMI, sex, chemotherapy type, and diabetic status did not contribute to the final model and were excluded during backwards regression.

In the second model (F (2, 134) = 16.66, p < .0001, r² = .20), older age (B = .096, 95% CI = .061 - .130, p < .001) was also associated with worse CIPN severity, as was larger BSA (B = .429, 95% CI = 1.340 - 4.478, p < .05). Waist circumference, chemotherapy type, diabetes and sex were non-significant factors in the final model (N.S.).
Table 7.4. Multivariate linear regression evaluating the association between patient and clinical variables, including measures of general and central obesity and CIPN severity (TNSc)

<table>
<thead>
<tr>
<th>Measure of general obesity (BMI and BSA)</th>
<th>Univariate</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-values</td>
<td>BMI</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>B (95% C.I.)</td>
<td>BSA (95% C.I.)</td>
</tr>
<tr>
<td><strong>&lt;0.001</strong></td>
<td>Exc.</td>
<td>2.409(.340-4.478)</td>
</tr>
<tr>
<td><strong>.018</strong></td>
<td>.030 (.001-.059)</td>
<td>.046</td>
</tr>
<tr>
<td>WHR</td>
<td>.204</td>
<td>--</td>
</tr>
<tr>
<td>Age (years)</td>
<td><strong>&lt;0.001</strong></td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td></td>
<td><strong>.008</strong></td>
<td>Exc.</td>
</tr>
<tr>
<td>Sex</td>
<td><strong>.005</strong></td>
<td><strong>.015</strong></td>
</tr>
<tr>
<td>Diabetic status</td>
<td><strong>.005</strong></td>
<td><strong>.015</strong></td>
</tr>
<tr>
<td>Chemotherapy type</td>
<td><strong>.008</strong></td>
<td><strong>.005</strong></td>
</tr>
<tr>
<td>RDI (%)</td>
<td>.154</td>
<td>--</td>
</tr>
<tr>
<td>Cumulative dose (mg/m²)</td>
<td>.154</td>
<td>--</td>
</tr>
<tr>
<td>Months post treatment</td>
<td>.181</td>
<td>--</td>
</tr>
</tbody>
</table>

*p*-values indicate significant univariate clinical factor included in multivariate models. To avoid violating the assumption of collinearity, BMI and BSA (uncapped) were evaluated in two separate models. Significant multivariates with B, 95% confidence intervals and *p*-values retained in the final model are indicated in bold. Exc.: Variables inputted into the multivariate model but excluded (*p*>.1) by backwards regression from the final models.
Discussion

This study aimed to evaluate if being overweight (BMI: ≥25kg/m²) was associated with worse symptomatic, clinical and functional CIPN following neurotoxic cancer treatment. Most of the cohort reported residual CIPN symptoms, with deficits also evident on clinical examination. Patients who were classified as overweight had significantly worse CIPN across symptomatic, objective clinical and functional outcomes compared to those with a normal BMI. In multivariate linear regression, older age, larger waist circumference and BSA were the main factors associated with CIPN. Diabetic status and BMI were significant on univariate analysis but failed to contribute to the final models.

Across western populations, obesity is highly prevalent with 71% of American and 67% of Australian adults having a BMI ≥25kg/m² (Australian Bureau of Statistics 2018). In the current Australian cohort, 63.8% of cancer survivors were overweight, with 29% having a BMI ≥30kg/m². Previously, 22-55% of paclitaxel and oxaliplatin treated patients have been classified as obese (BMI: ≥30kg/m²) (Barginear et al. 2019, Greenlee et al. 2017, Petrovchich et al. 2019) likely reflecting heterogeneity in obesity rates between international populations (WHO 2020). Though BMI is used widely to report obesity, waist circumference has been highlighted as a more reliable estimator of adiposity and predictor of chronic diseases such Type 2 diabetes (WHO 2020, Ross et al. 2020). In the United States, more than 70% of women over the age of 50 exceed the waist circumference threshold (≥80 cm) for abdominal obesity, with the rate increasing with age (Li et al. 2007, Fryar et al. 2018). Similarly, 83% of Australian women over the age of 65 years were classified as having abdominal obesity (Australian Bureau of Statistics 2018), comparable to the rates of elevated waist circumference in the current female predominant study (85.2%).
Symptomatic, clinical and functional CIPN outcomes for overweight cancer survivors

Comparable with other studies utilizing patient report (Hershman et al. 2018, Greenlee et al. 2017), the majority of the cohort (78.5%) described some level of residual CIPN symptoms, with most patients expressing greater severity of symptoms in the feet. Correspondingly, a large proportion of patients demonstrated deficits in clinical examination suggestive of sensory predominant neuropathy, consistent with previous reports (Park et al. 2011b, Timmins et al. 2020b). Overweight patients (BMI: ≥25kg/m^2) were more likely to report CIPN symptoms, describe greater lower limb severity and worse overall symptom burden. Consistent with these observations, obesity has been identified as a predictor of patient reported CIPN symptom burden in a large prospective study of breast cancer patients (Greenlee et al. 2017).

Similarly, patients reporting lower limb CIPN following platinum or taxane treatment were more likely to be obese (Winters-Stone et al. 2017). However patient report alone may be confounded by the increased mechanical force exerted on weight bearing extremities in overweight individuals, potentially influencing patient perception of CIPN symptoms (Petrovchich et al. 2019). Consequently, additional CIPN assessment may mitigate the limitations of unimodal patient report. While two small studies have previously utilised clinical examination to quantify CIPN in paclitaxel treated breast cancer patients, BMI was not found to be an independent risk factor for CIPN incidence (Ghoreishi et al. 2018, Robertson et al. 2018). Further, there was no evidence of worsened vibration, cold perception or light touch in objective examination of sensation in overweight cancer survivors with CIPN (Petrovchich et al. 2019). Similarly, this study did not identify measurable differences in sensory function in upper or lower limbs. However, significant differences in a validated clinical assessment tool (TNSc) for CIPN were identified, suggestive of objective neurological deficits.

Importantly, this study assessed functional impairment associated with obesity and CIPN utilising objective assessment including quantifying balance impairments. In the present cohort, overweight patients demonstrated increased postural sway, an objective indicator of balance deficits.
(Sturnieks et al. 2011). Consistent with these findings, overweight survivors with CIPN have previously reported significantly greater balance deficits compared to patients with CIPN and a normal BMI, with obese survivors also demonstrating worse balance scores on functional scales (Petrovchich et al. 2019). Similarly, in the present cohort functional impairment in the hands were reflected in increased peg board times, indicating reduced manual dexterity for overweight patients. In addition to greater functional burden associated with increased CIPN severity, being overweight may exacerbate functional deficits, with balance impairment reported to occur in overweight individuals without cancer (Frames et al. 2018). Moreover, there is growing evidence supporting exercise as a strategy to ameliorate CIPN symptoms and related balance deficits (Zimmer et al. 2018, Kleckner et al. 2018, Mccrary et al. 2019a). Though physical activity levels were not recorded in this study, overweight individuals are less likely to meet recommended guidelines for physical activity, potentially forgoing some benefits for CIPN (Australian Bureau of Statistics 2008). Given that cancer survivors with CIPN are nearly twice as likely to experience falls (Winters-Stone et al. 2017, Mccrary et al. 2019b), overweight individuals experiencing symptoms may be at particular risk and may benefit from supportive services such as referrals to occupational therapists and physiotherapists.

**Factors associated with CIPN severity**

In the present study, older age, larger waist circumference and BSA were the main factors associated with CIPN. Diabetic status and BMI were significant on univariate analysis but failed to contribute to the final models. Multiple previous studies have demonstrated more severe patient reported, clinician graded and objective CIPN with older age (Park et al. 2017a, Barginear et al. 2019, Robertson et al. 2018). Similarly, large population studies have identified obesity based on BMI as an independent risk factor for CIPN (Barginear et al. 2019, Song et al. 2017, Greenlee et al. 2017), though these findings are not universal (Schneider et al. 2012, Furlanetto et al. 2016). Variability may be partly attributed to many earlier studies utilising unimodal CIPN assessment such as a 4-point clinical-grading scale, with
most analyses being conducted retrospectively. Interestingly, in the present study waist circumference and BSA, not BMI, were associated with greater CIPN severity based on a validated clinical assessment tool (TNSc).

Waist circumference is a reliable measure of adiposity and indicator of poor body composition, which may influence the pharmacokinetics of neurotoxic treatment (Rankinen et al. 1999, WHO 2020). Accordingly, when BSA was included in the model, waist circumference was no longer a significant predictor. BSA is used to calculate chemotherapy dose as it mitigates variability in adiposity distribution to a greater degree than BMI (Bray et al. 2014). However, body composition may impact the pharmacokinetics of cancer treatment. Specifically, individuals with greater adiposity may be exposed to neurotoxic agents for a longer period (Dijksterhuis et al. 2019) as lipophilic agents, including paclitaxel and oxaliplatin, accumulate in adipose tissue and have the potential to be re-released (Gérard et al. 2016, Li et al. 2015). Moreover, as anti-cancer drugs are generally metabolized within lean metabolic tissues, patients with larger BSA and lower lean body mass may essentially receive higher doses of neurotoxic cancer treatment and consequently experience greater dose-limiting toxicities such as neuropathy (Ali et al. 2016). While CIPN prevalence and severity are broadly associated with cumulative dose (Park et al. 2013), surprisingly, relative dose intensity was not a significant predictor in either model, suggesting that individual characteristics may be playing a more significant role than crude measures of dose. As such, more accurate evaluation of body composition, and subsequent normalizing of dosing could assist in reducing toxicity (Ali et al. 2016). Though imaging methods such as computed tomography scans provide an accurate estimation of body composition (Dijksterhuis et al. 2019), waist circumference may offer an alternative estimation of centralised adiposity and body composition which can be easily implemented in routine clinical practice.
In this study, diabetic status was not associated with CIPN severity in the final models. Though some investigations have identified diabetes as a risk factor for CIPN (Hershman et al. 2016, Ottaiano et al. 2016, Kus et al. 2016), others have failed to find an association (Simon et al. 2017, Winters-Stone et al. 2017, Robertson et al. 2018, Brown et al. 2019). However, diabetes is a common exclusion criterion for many CIPN trials and may be underrepresented as a risk factor. Moreover, the presence of diabetic neuropathy, time of diagnosis or extent of diabetic control may better characterise the contribution of diabetes to CIPN vulnerability and needs to be addressed in future trials.

Though the contribution of glycaemic status to CIPN risk needs to be further elucidated, there is a growing body of evidence for obesity-related neuropathy amongst normoglycemic obese individuals without cancer (Callaghan et al. 2016a, Callaghan et al. 2020b, Callaghan et al. 2016b). Specifically, larger waist circumference has been associated with neuropathy risk in normoglycemic obese individuals independent from BMI (Callaghan et al. 2020b), with inflammatory processes suggested as the primary pathophysiological mechanism (Klöting et al. 2014, O’Brien et al. 2017). It is also possible that systemic metabolic and inflammatory processes linked to centralised obesity mediate the association with neuropathy risk (Callaghan et al. 2020b), however these mechanistic relationships require further investigation in neurotoxic-treated cancer population.

Given the prevalence of obesity, overweight patients represent a large proportion of cancer survivors who may be particularly affected by CIPN and benefit most from supportive services, such as referrals to exercise physiologist, and occupational and physiotherapists. The factors identified in this study should be verified in large-scale trials, conducted longitudinally with baseline neuropathy assessment to confirm whether obese whether obese patients are impacted more severely by CIPN. Nevertheless, this study highlights the potential utility of routinely measured patient characteristics which may contribute to an individual’s CIPN risk profile may assist with informing treatment decisions. Specifically, easily accessible data regarding general
and central obesity status may aid in formulating a personalised approach to treatment through
more nuanced dosing and by identifying patients warranting closer neurological monitoring to
detect developing impairment and alter regimen prior to irreversible long term clinical disability.
Chapter 8

Summary and Conclusions
The studies contained in this thesis have utilised multimodal CIPN assessment to investigate treatment specific CIPN profiles and explore patient characteristics which may contribute to CIPN severity.

These studies have provided evidence for the variability in the clinical presentation of CIPN and discrepancies between the clinical definition, objective assessment, and patient experience, highlighting the need for a multimodal approach. Furthermore, these studies have elucidated the phenotypic profile and longitudinal development of CIPN in a homogenously treated cohort of paclitaxel treated patients and assessed the role of dose modification on neuropathy outcomes, with variation in outcomes alluding to a role for individual risk factors. Finally, the role of risk factors on symptomatic, objective, and functional CIPN outcome measures were investigated.

In chapter 3, bilateral neuropathy assessments including clinical examination, NCS and patient questionnaires revealed discrepancies between the patient experience and objective CIPN assessment. Specifically, 35% of patients indicated side-to-side symptom asymmetry and 29% of the cohort demonstrated bilateral differences on objective clinical assessment. However, objective evidence of asymmetry was not identified in clinical or neurophysiological assessments in those reporting asymmetrical side-to-side symptoms. Similarly, patients reporting differences in symptom severity between the hands and feet were just as likely to present with comparable assessments as to demonstrate objective discrepancies, further suggesting discordance between patient experience and objective assessment. These discrepancies highlight variability in clinical presentation of taxane-induced neuropathy, with some patients reporting symptoms that were discrepant with the expected symmetrical distribution of toxic neuropathy and emphasising the need to include multimodal CIPN assessment to fully capture the patient experience.

To further investigate the phenotypic profile of taxane-induced neuropathy and examine the clinical definition of distal symmetric polyneuropathy, extensive bilateral clinical and
electrophysiological assessments were undertaken (chapter 4). Importantly, though NCS were consistent with a sensory predominant axonal neuropathy, features more typical of entrapment neuropathy were also present in >50% of patients. These features were not associated with overall severity of CIPN or clinical risk factors and potentially represent a mononeuropathy that may manifest with taxane treatment in a subgroup of patients. This study demonstrated the importance of understanding the variability in the CIPN presentation to guide dose modification while limiting premature cessation of effective cancer treatment in patients with less severe or localised neurological sequelae.

Breast cancer survivors represent the largest cohort of female cancer survivors (Jemal et al. 2019). Given the widespread use of weekly paclitaxel in the adjuvant treatment of early breast cancer it is important to understand the development and long term neurological sequelae associated with this treatment. Further, the role of dose-modification on neuropathy outcomes is ill-defined despite it being the only recommended strategy for mitigating CIPN (Loprinzi et al. 2020). The development of CIPN and its impact on post treatment outcomes have not been adequately explored, with a lack of comprehensive quantitative CIPN assessment measures, insufficient follow-up time and treatment heterogeneity common limitations of previous studies (Rivera et al. 2017). Subsequently, a cohort of homogenously treated breast cancer patients were prospectively assessed to evaluate neuropathy development from weekly paclitaxel treatment and examine the impact of dose-reduction on post-treatment neuropathy outcomes (chapter 5).

Significant neuropathy was present by mid-treatment across patient-reported, clinical, and objective neurophysiological assessments, suggesting the need for closer monitoring for some individuals. CIPN prevalence and severity increased over the treatment course peaking at the end of treatment. Limited recovery was observed during follow-up, with significant neuropathy being maintained up to 12 months post completion, identifying CIPN as a persistent sequela which may impact quality of life and require appropriate supportive services.
Interestingly, when evaluating the role of dose modification, patients who received dose reduction had worse patient and clinical neuropathy outcomes compared to those who received the full dose three months post-treatment. Specifically, those who ceased treatment early demonstrated the worse deficits despite receiving the lowest cumulative dose, however those who ceased later in the treatment did not differ significantly from those receiving the full dose. Though paclitaxel-induced neuropathy is generally considered a dose-dependent neuropathy, these findings suggest that dose reduction does not necessarily lead to more favourable neuropathy outcomes, with individual risk factors likely important in addition to cumulative dose. This study provided a comprehensive understanding of the clinical manifestations and outcomes of weekly paclitaxel-induced neuropathy which may provide clinicians with resources to better inform treatment decisions and counsel patients. Further, this study highlighted the variation in response to dose modification on neuropathy outcomes, emphasising the need to identify individual risk factors.

Chapter 5 highlighted the need to understand patient characteristics which may contribute to an individual's risk profile and dose response. Though many factors have been postulated as contributing to CIPN vulnerability, much discord exists in the currently literature. While some have suggested that obesity and diabetes may be probable risk factors for CIPN, due to their independent association with nerve dysfunction, there remains a lack of clear evidence. To evaluate the literature surrounding metabolic risk factors and their association with CIPN a systematic review was undertaken (chapter 6). Twenty-six studies were included, with an overall incidence of neuropathy was 16.9% to 89.4%, emphasising the wide range of reported CIPN incidence in the literature. Additionally, large variation was observed in the patient populations, treatment type, dose and regimen, as well as inconsistency in the measurement and definition of CIPN, and potential risk factors. Nevertheless, obesity had the most consistent patient-oriented evidence as a risk factor for CIPN, with only a limited number of studies supporting an association between low physical activity and greater CIPN risk.
Moderate evidence suggested diabetes did not increase CIPN incidence or severity, however diabetes was a common exclusionary criterion for many CIPN studies, which may limit the ability to understand its potential as a risk factor. This review identified potential risk factors which are prevalent in the general population and further stresses the need for sensitive outcome measures to be used in large scale clinical trials investigating CIPN risk factors.

Based on the systematic review of the literature, the role of obesity on CIPN outcomes was investigated (chapter 7). Overweight cancer survivors had significantly worse CIPN across symptomatic, objective clinical and functional outcomes compared to those with a normal BMI. When looking at predictors of CIPN severity, older age, larger waist circumference and larger BSA were associated with worse CIPN. Diabetes and BMI were significant on univariate analysis but not in the final models, suggesting that body composition may be playing an important role in mediating CIPN risk, be it through variation in dosing and treatment metabolism or inflammatory processes associated with obesity. Further, this study highlighted that overweight individuals represent a large proportion of cancer survivors who may be particularly affected by CIPN, warranting closer monitoring and referral to supportive services.

**Future directions**

The number of cancer survivors living with long-term side effects of treatment such as CIPN is likely to increase with continued implementation of successful cancer treatments. Understanding the symptoms and time course of CIPN, as well as patient risk profiles are important factors for ensuring effective treatment management and long-term quality of life in the cancer survivor population. The work contained in this thesis identified discrepancies between the patient experience, clinical impression and objective CIPN assessment, highlighting the importance of comprehensive, multimodal CIPN assessment to help in the early identification of nerve damage. Further, specific CIPN phenotypes were explored elucidating variations from
the clinical definition of CIPN. Finally, patient characteristics which may contribute to the CIPN risk profile where identified.

Building on these findings, future prospective studies will focus on establishing the optimal, comprehensive assessment package for assessing CIPN with high reliability, validity and sensitivity that will be suitable for use in the research settings. Incorporating some of the most effective measures into an abbreviated assessment package would allow for effective implementation in the clinic. Specifically, incorporating patient reported outcome measures and objective clinical examination may assist with enhanced clinical screening, better identifying patients warranting dose modification and improving CIPN management.

Comprehensive and reproducible assessments will also assist with exploring neuroprotective strategies, act as a sensitive predictor of long-nerve damage and aid in the identification of CIPN risk factors. In addition to the risk factors identified in this thesis, the elucidation of other patient and clinical factors and the further exploration of pharmacogenomics which may determine inherited vulnerability for CIPN, will help to build a more comprehensive understanding of an individual’s CIPN risk profile and assist in formulating individualised treatment strategies.

Though a more comprehensive understanding of the CIPN phenotype associated with taxane agents was presented as part of this thesis, the natural history and mechanism of neuropathy differ between various neurotoxic treatments (Zajączkowska et al. 2019). Specifically, treatments used in haematological malignancies, such as bortezomib, thalidomide and vinca alkaloids, demonstrate varying phenotypes including higher rates of small fibre involvement and more frequent reports of painful symptoms compared to platinum and taxane agents (Timmins et al. 2019). Future investigations into these agents may elucidate alternate mechanisms of chemotherapy-induced neurotoxicity and potentially identify subgroups of patients with painful symptoms which may respond to neuropathic pain medications.
The identification of early CIPN, utilising appropriate assessment tools, will allow for the management of patients at risk of developing long-term deficits. Additionally, understanding CIPN risk profiles and treatment specific neuropathy phenotypes will also assist with treatment decisions, and identification of patients who require intervention and supportive care, enabling personalised medicine and subsequently improving clinical outcomes while reducing patient burden from long term side effects.
Appendices
### Supplemental table 1

Original Medline Search strategy (Adapted for other searches)

<table>
<thead>
<tr>
<th>Database</th>
<th>Search terms for CIPN</th>
<th>Physical activity</th>
<th>Diabetes</th>
<th>Body composition</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline</td>
<td>Chemotherap*.mp. Paclitaxel/OR paclitaxel.mp OR Taxol.mp OR Docetaxel/OR docetaxel.mp OR taxane.mp OR Taxoids/OR Taxoid*.mp OR Albumin-Bound Paclitaxel/OR Albumin-Bound Paclitaxel.mp OR Abraxane.mp OR taxane derivativ*.mp OR Oxaoliplatin/OR Oxaoliplatin/.mp OR Cisplatin/OR Cisplatin.mp. OR Platinum/OR Platinum.mp OR Platinum compounds/OR Platinum compounds.mp OR Vincristine/OR Vincristine.mp Vinca/OR Vinca.mp OR Vinca alkaloids/OR Vinca alkaloids.mp OR Thalidomide/OR Thalidomide.mp OR Lenalidomide/OR Lenalidomide.mp OR Pomalidomide/OR Pomalidomide.mp</td>
<td>Exercise/OR exercise*.mp. OR physical activit*.mp. OR kinesiotherapy.mp. OR Exercise Therapy/OR exercise therap*.mp.</td>
<td>Diabetes Mellitus/ OR Diabetes mellitus.mp. OR Diabetes.mp. OR Diabetes Mellitus, Type 2/ OR Diabetes Mellitus, Type 2.mp. OR non-insulin dependent diabetes mellitus/ OR non-insulin dependent diabetes mellitus.mp. OR Diabet*.mp. OR Hyperglycemia/ OR Hyperglycemia.mp.</td>
<td>Obesity/ OR Obesity.mp. OR Body Weight/ OR Body weight*.mp. OR Obesity, Abdominal/ OR Abdominal obesity.mp. OR Body Mass Index/ OR Body mass index.mp. OR BMI.mp. OR Body Composition/ OR Body composition.mp. OR Lean body weight.mp. OR Lean body mass.mp. OR Body Surface Area/ OR Body surface area.mp. BSA.mp.</td>
<td>Huma n 1980 - current, English TITLE-ABS-KEY</td>
</tr>
</tbody>
</table>
OR Bortezomib/
OR Bortezomib.mp
OR ixazomib.mp
OR carfilzomib.mp
OR ixabepilone.mp
OR Epothilones/
OR epothilone derivative.mp.
AND
Chemotherapy?induced peripheral neuropath*.mp OR
Neurotoxicity Syndromes/ OR
neuropath*.mp OR
neurotoxic*.mp OR
neurotoxic disorder*.mp. OR
CIPN.mp OR
Neuralgia*.mp. OR
neurotoxicity*.mp.
OR neuropathic pain*.mp OR
Neuralgia/ OR
Neuralgia*.mp. OR
peripheral neuropath*.mp OR
Peripheral Nervous System Diseases/
**APPENDIX 2** The Impact of Obesity on Neuropathy Outcomes for Paclitaxel and Oxaliplatin-treated Cancer Survivors

*Supplementary Table 1.* Comparison between paclitaxel and oxaliplatin treated cohorts for demographic, clinical factors and obesity measures using Chi sq for categorical and independent samples t-test for continuous variables.

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel (n= 245)</th>
<th>Oxaliplatin (n= 134)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Years)</strong></td>
<td>57.6±1.2</td>
<td>57.1±1.7</td>
<td>N. S</td>
</tr>
<tr>
<td><strong>Mean ±SE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time since treatment (months)</strong></td>
<td>7.0±0.4</td>
<td>5.4±0.4</td>
<td>&lt;.05</td>
</tr>
<tr>
<td><strong>Mean ±SE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relative dose intensity (%)</strong></td>
<td>88.3±1.2</td>
<td>83.3±2.0</td>
<td>&lt;.05</td>
</tr>
<tr>
<td><strong>Mean ±SE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Female</strong> (% , n)</td>
<td>97.1 (238)</td>
<td>42.5 (57)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td><strong>Diabetics</strong> (% , n)</td>
<td>8.9 (21)</td>
<td>9.92 (13)</td>
<td>N. S</td>
</tr>
<tr>
<td><strong>Abnormal BMI ≥25kg/m²</strong> (% , n)</td>
<td>61.22 (150)</td>
<td>65.71 (161)</td>
<td>N. S</td>
</tr>
<tr>
<td><strong>Obese: ≥30kg/m²</strong> (% , n)</td>
<td>32.5 (79)</td>
<td>23.1 (31)</td>
<td>N. S</td>
</tr>
<tr>
<td><strong>Abnormal BSA</strong> (% , n)</td>
<td>81.4 (197)</td>
<td>75.4 (101)</td>
<td>N. S</td>
</tr>
<tr>
<td><strong>Abnormal Waist circumference+</strong> (% , n)</td>
<td>88.3 (91)</td>
<td>78.3 (36)</td>
<td>N. S</td>
</tr>
</tbody>
</table>
Abnormal waist to hip ratio*  91.3 (94)  71.7 (33)  <.05

* Additional anthropometric measurements were taken in a subset of patients during CIPN assessments (n=149).
**Supplementary Table 2.** A comparison of CIPN outcomes measures between paclitaxel and oxaliplatin treated patients

<table>
<thead>
<tr>
<th>Paclitaxel (n=245)</th>
<th>Oxaliplatin (n=134)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient symptom report</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACT/GOG-NtX13</td>
<td>43.56±.66</td>
<td>39.15±.85</td>
</tr>
<tr>
<td>Range</td>
<td>16-52</td>
<td>21-52</td>
</tr>
<tr>
<td><strong>Clinical and sensory assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNSc</td>
<td>3.79±.24</td>
<td>4.75±.29</td>
</tr>
<tr>
<td>Range</td>
<td>0-12</td>
<td>0-14</td>
</tr>
<tr>
<td>Von frey (mN)</td>
<td>.58±.11</td>
<td>3.78±.94</td>
</tr>
<tr>
<td>Range</td>
<td>.12-11.31</td>
<td>.12-90.51</td>
</tr>
<tr>
<td>Two point (mm)</td>
<td>12.14±.31</td>
<td>11.54±.43</td>
</tr>
<tr>
<td>Range</td>
<td>4-15</td>
<td>2-15</td>
</tr>
<tr>
<td>Functional assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Peg (Sec)</td>
<td>69.81±1.53</td>
<td>87.34±3.24</td>
</tr>
<tr>
<td>Range</td>
<td>40.06-173.30</td>
<td>49.80-201.27</td>
</tr>
<tr>
<td>Postural sway path length (mm)</td>
<td>714.87±25.13</td>
<td>896.15±35.16</td>
</tr>
<tr>
<td>Range</td>
<td>358.00-1683.00</td>
<td>232.00-1533.00</td>
</tr>
</tbody>
</table>


ovarian cancer survivors: Results from the population-based profiles registry." 


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