Curriculum Vitae

Israel N. Akpadiaha

Education

Aug. 2008 – Dec. 2016 University of MD Baltimore, MD
* Doctor of Philosophy (Ph.D.)

Aug. 2005 – Dec. 2007 University of MD Baltimore, MD
* Master of Science (M.S) – Nurse Anesthesia Cum Laude

Jan. 1998 – May 2001 Liberty University Lynchburg, VA
* Bachelor of Science in Nursing (B.S.N) Cum Laude

Professional Experience

Jan. 2011 – Date Johns Hopkins School of Medicine/ Howard County Anesthesia Associates Baltimore, MD

Certified Registered Nurse Anesthetist
Perform duties of a CRNA as described below

Member – Institutional Review Board at Howard County General Hospital, Columbia MD

* Review studies to be conducted at the hospital for scientific rigor, relevance and feasibility.
* Review, approve and monitor safety procedures and processes associated with scientific studies conducted at the hospital to ensure adequate appropriate patient protections.
* Review, approve and monitor procedures and processes which ensure protection of vulnerable populations and children involved in scientific studies.
* Evaluate the availability and facilitate the utilization of necessary and available resources for the conduct of relevant scientific studies.
* Provide feedback and report to hospital administration on the conduct of scientific studies and use of hospital facilities for such studies.
* Co-ordinate and collaborate with scientists to facilitate and ensure scientific studies conducted at hospital meet local, state and national patient safety standards.

June 2008 – July, 2011 University of MD Medical Center Baltimore, MD

Certified Registered Nurse Anesthetist (CRNA)
In collaboration with anesthesiologist colleagues, proficiently and safely:

* Administer specific types of anesthesia for patients across the life-span, including parturient patients.
* Perform pre-anesthesia evaluation and preparation.
* Administer general anesthesia including adjunct drugs and regional anesthesia/analgesia techniques.
* Administer ancillary drugs and fluids to maintain physiological hemostasis and prevent or treat emergencies during the peri-anesthetic period.
* Utilize basic and advanced airway techniques during the pre-anesthetic, peri-anesthetic and post-anesthetic periods.
* Perform tracheal intubation and extubation.
* Place intra-arterial and central venous catheters.
* Perform regional anesthesia including spinal and epidural anesthesia.
* Manage mechanical ventilation and oxygen therapy.
* Initiate and modify therapies including drug and pain therapy.
* Perform post-anesthesia care and discharge when necessary.
* Provide consultation, management and implementation of respiratory and ventilatory care.
* Accurately document patient care and billing information on both paper and computerized documentation systems
* Mentor and orient new CRNA staff and student anesthetists

June 2004 – July 2006 Laurel Regional Hospital Laurel, MD

Nurse Clinician – Emergency Department

* Provide holistic care for critically ill and injured patients as well as those presenting with various forms of emergency.
* Safely and accurately administer medications through all routes.
* In conjunction with established First Responders, provide emergency care to patients involved with various forms of regional disasters, including vehicular accidents and food poisoning.
* Effectively assess patients and in conjunction with other health care team members, provide effective treatments to various patient ailments.
* Effectively delegate jobs and responsibilities to and supervise support support associates.
* Effectively document patient care.
* Member of committee responsible for the functional design of the emergency department during the hospital's expansion.

Sept. 2003 – Nov. 2003 Johns Hopkins Hospital Baltimore, MD

Nurse Clinician – Interventional Cardiology/Radiology Center

* Provide pre-procedural care, including assessment, placement of intravenous lines and administration of pre-procedure medications.
* Safely provide conscious sedation, continuously monitor and manage patients during various interventional cardiology/radiology procedures including but not limited to percutaneous transluminary coronary

angioplasty; artherectomies; the placement of stents in various blood vessels; the placement of intra-aortic balloon pumps; the placement of various types of vascular access devices; the administration of intra-arterial, organ-specific, target-specific chemotherapeutic and thrombolytic drugs; the excision and drainage of abscesses; post-transplant organ and tissue biopsies; insertion, changing and removal of various tubes and drains from various organs as well as pre-diagnostic and post-diagnostic imaging for surgical patients.

* Manage patients enrolled in various research projects and assist with the collection of research data on new and experimental therapies as well as physiological exploration for patients presenting with various coronary artery and renal artery diseases.
* Administer medication through all routes and efficiently document patient care.
* Provide monitoring, various medications and management for critically ill patients, including patients on ventilators and concomitant vasoactive drips requiring various interventional cardiology/radiology procedures, as well as placement of various vascular access devices.
* Collaborate with and assist physicians during various interventional cardiology/radiology procedures.
* Provide post-procedure monitoring including sheath monitoring for patients recovering from various procedures.
* Safely transfer patients requiring further monitoring to various telemetry or intensive care units.
* Provide procedure information and discharge teaching to patients undergoing various interventional cardiology/radiology procedures, including cardiac catheterization for balloon angioplasty and stent placement as well as insertion and removal of various tubes, drains and vascular access devices.

July 2001 – July 2003 Johns Hopkins Hospital Baltimore, MD

<u>Nurse Clinician, Primary Nurse, Unit Preceptor – Neuroscience ICU</u>

* Provide holistic patient care for critically ill, injured and post-operative patients in the Neuroscience Critical Care Unit.
* Manage complex patients on ventilators, various hemodynamic and intracranial pressure monitoring devices with concomitant multiple vasoactive drips from admission to discharge from the intensive care unit.
* Manage patients on and assist with induction of pentobarbituate coma and various levels of sedation including deep sedation using propofol drip.
* Formulate, co-ordinate and in conjunction with an interdisciplinary health care team, execute care plans for complex and critically ill patients from admission to discharge from the intensive care unit.
* Effectively present patients and participate in interdisciplinary rounds, advocate on patients' behalf, assist physicians with complex procedures,

perform complex wound care and dressing changes, safely administer medications through all routes and document patient care on both paper and computerized systems.

* Effectively utilize hospital resources to manage complex crisis situations involving families of critically ill patients.
* Effectively collaborate with the Transplant Resource Center in the process of organ donation, procurement and disbursement.
* Participate in and assist with the collection of relevant data for various clinical research projects, including the formulation and testing of new, modified and alternative treatment modalities
* Precept, teach and mentor new graduate nurses, nursing students and clinical technicians alike into their new roles.
* Member of education team responsible for organizing and teaching classes, as well as training Clinical Technicians in the Neurosciences Department.
* Effectively delegate jobs and responsibilities to support associates.
* Occasionally function as the Charge Nurse, responsible for the smooth operations of a 10-bed section of the Neuroscience Critical Care Unit.

Volunteer Activities

2007 – Present Diversity in Nurse Anesthesia Mentorship Program Mickelton, NJ

* Mentor minority student anesthetists during their nurse anesthesia education.
* Conduct and facilitate share days for aspiring minority nurse anesthesia students.
* In conjunction with various nurse anesthesia program directors, conduct and facilitate information sessions and airway workshops around the country to expose minority critical care nurses, nursing students and aspiring nurse anesthesia students to the anesthesia profession.
* Provide peer-assistance and wellness programs to student nurse anesthetists to help facilitate success during their education.
* Sponsor current and aspiring student nurse anesthetists to various anesthesia conferences.

Certifications & Licensures

Advanced Cardiac Life Support (ACLS)
Cardio-pulmonary resuscitation (CPR)
Current unrestricted Registered Nurse License in MD
Current unrestricted CRNA Licensure in MD
Certified Registered Nurse Anesthetist (CRNA)

Professional Memberships

American Association of Nurse Anesthetist (AANA)
Maryland Association of Nurse Anesthetists (MANA)

Awards

Fellow – Graduate Assistance in Areas of National Need Federal Fellowship (2008 – 2009 U. of MD. School of Nursing)
Advanced Education Nursing Traineeship Grant recipient (2005 –2007; 2010 - 2012)
Honors Scholar (2001), Liberty University
Minority Student Achievement Award (2001), Liberty University
Student Nurse of the Year (2001), Virginia Nurses' Association
National Collegiate Minority Leadership Award (2001)

Abstract

Title: The Use of Current Perception Threshold for the Assessment of Oxaliplatin-Induced Peripheral Neuropathy

Israel Akpadiaha, Doctor of Philosophy
Dissertation directed by Dr. Kathleen Griffith, PhD, RN.

Background: Colorectal cancer (CRC) is a common malignancy, and up to 80% of patients diagnosed receive chemotherapy. Oxaliplatin is the principal chemotherapy agent for the treatment of CRC, and yet the associated oxaliplatin-induced peripheral neuropathy (OIPN) affects sensory fibers and is a treatment-limiting factor. OIPN reduces quality of life (QoL) and is associated with neuropathic pain (NP). As no effective treatment is available, improved early assessment of OIPN is needed. Current perception threshold (CPT) is a promising approach that uses sine-wave current electrical stimulus delivered at specific frequencies to elicit responses from peripheral nerves and may aid in OIPN identification.

Purpose: The purpose of this study was threefold: 1) to compare CPT with validated quantitative sensory testing (QST) clinical tests in assessing sensory fiber function; 2) to compare CPT with provider administered National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTC-AE) for identification of OIPN; and 3) to describe the relationship between NP measured by Neuropathic Pain Scale (NPS) and QST and their differential impact on QoL (FACT-G).

Methods: A correlational descriptive design was used and a secondary analysis conducted using data from the Genetic Correlates of OIPN study. A total of 19 participants were enrolled and assessed at baseline, following 500mg/m^2 of oxaliplatin, and upon oxaliplatin completion. Bivariate linear mixed models were used to account for repeated assessments clustered within patients.

Results: An association between certain QST measures and CPT 2000Hz was identified (Vibration: β=-44.55, p=0.045; mechanical detection: β=269.59, p=0.008). CPT 2000 Hz and 250 Hz were associated with warm detection threshold (β=9.0, p=0.030 and β=4.24, p=0.027, respectively). There was also a positive association between neuropathic pain severity (NPS) and QoL [FACT-G (β=0.276, p<0.016)].

Conclusion: The association between CPT and currently documented methods of OIPN assessment was limited. Furthermore, the positive association between NP and QoL requires additional exploration as it contradicts published data. Larger studies are needed to explore further if CPT is useful for assessment of OIPN.

The Use of Current Perception Threshold for the Assessment of Oxaliplatin-Induced Peripheral Neuropathy

by
Israel Akpadiaha

Dissertation submitted to the faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
Of the requirements for the degree of
Doctor of Philosophy
2016

Dedication

This dissertation is dedicated to my beloved Late father, Friday Akpan Akpadiaha and my beloved mother, Phebe L. Akpadiaha, who, understanding the importance, made education and learning so cool to my siblings and I from a very young age, and then sacrificed everything to ensure that we received the best education they could possibly afford, to develop that love for learning and knowledge. To my father who could teach anything to anyone and to my mother who could organize knowledge and information like no one else, I am eternally grateful. If I could do life all over again, I will choose you both as my parents – every time.

Acknowledgements

I give all the glory to God for His hand of providence throughout my entire life and particularly over the course of my education in the United States. I would like to express my deepest gratitude to the members of my dissertation committee for their guidance and commitment. I want to thank Dr. Naomi Horiba, MD for standing in the gap and providing medical guidance during patient assessments. I want to thank Dr. Cynthia Renn, for her guidance during my comprehensive examination and direction with quantitative sensory testing and Dr. S. Zhu for guiding me through the complex data analysis required for this study. I am very grateful to Dr. Susan G. Dorsey, for providing me the opportunity to study and work under her mentorship in her laboratory and for the wonderful exposure and opportunities that came with that privilege. I am also grateful for the graduate research assistantships, which helped fund my education. I am particularly grateful to Dr. Meg Johantgen for her persistence, for believing in me and for providing me the opportunity and resources to succeed. It would certainly not be an overstatement to say that I would not have completed this project without her support. Lastly, I cannot begin to express in words, the gratitude I have for Dr. Kathleen Griffith, who patiently directed my dissertation. I am so grateful for her patience, guidance, perseverance and understanding. I am most grateful for her KIND WORDS and the courtesy that she extended to me, particularly during some very difficult times, especially those times when I wanted to throw in the towel. I want to extend my gratitude to Natalie Criado, Books Dubose and Khristy Bozylinski from Dr. Susan G. Dorsey's lab, who worked tirelessly with me to perform assessments and collect data from study participants.

I want to thank my parents and siblings and especially my aunt Elizabeth Onyebuchi for their wonderful support as well as the members of my church family who prayed relentlessly for my success. I want to also thank my army of friends, who have provided me incredible support along the way and have tolerated my many absences. I am particularly grateful to Dennis Kahiro Munene for his encouragement, Jamie Hatcher, CNM for volunteering to read, edit and provide valuable feedback on short notices and Matthew Barstead who provided me with excellent tutorship in linear mixed modeling.

I want to thank my colleagues in the Department of Anesthesiology at Howard County General Hospital who made many adjustments and changes to their work schedules to accommodate my needs. I am particularly grateful to the department chief, Dr. Bernard Marquis, MD for his unconditional support during my entire PhD studies.

Lastly, but very importantly, I want to thank all the patients who participated in this study and who gave of themselves, despite the challenges of cancer diagnosis and treatment, to alleviate the suffering of future patients. I am particularly grateful to participant 002, who until her passing, remained committed to this study and to her family for the joy and focus they brought to my research, despite incredibly challenging personal circumstances. I will forever remain grateful for the constant, inspiring reminder they provided, of why work like this, though challenging, is important.

TABLE OF CONTENTS

LIST OF TABLES

TABLE OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Meaning
AP	Action Potential
CDT	Cold detection threshold
CIPN	Chemotherapy-induced neuropathy
CIPNAT	Chemotherapy-Induced Neuropathy Assessment Tool
CPT	Cold pain threshold
DH	Dorsal horn
DRG	Dorsal root ganglia
DTR	Deep Tendon Reflexes
FACT-G	Functional Assessment of Cancer Treatment - General
FACT GOG/Ntx	Functional Assessment of Cancer Treatment/Gynecologic Oncology Group – Neurotoxicity specific
HPT	Heat pain threshold
HRQoL	Health-related Quality of Life
ICC	Intra-class coefficient
IENFD	Intra-epidermal nerve fiber density
LMM	Linear Mixed Modeling
MDT	Mechanical detection threshold
NCI-CTC(AE)	National Cancer Institute Common Toxicity Criteria (for Adverse Events)
NCS	Nerve conduction studies
NP	Neuropathic Pain

NPS	Neuropathic Pain Scale
OIPN	Oxaliplatin-Induced Peripheral Neuropathy
OIPN-NP	OIPN-associated NP
PRQs	Patient-Reported Questionnaires
PAFs	Peripheral Afferent Fibers
QoL	Quality of Life
QST	Quantitative Sensory Testing (or Tests)
TNS©	Total Neuropathy Score scale – Original version
TNSc©	Total Neuropathy Score scale – clinical version
TNTP	The Neuromatrix Theory of Pain
VPT	Vibration perception threshold
WDR	Wide dynamic range
WDT	Warm detection threshold

CHAPTER 1

BACKGROUND AND SIGNIFICANCE OF STUDY

1.1. Oxaliplatin-induced peripheral neuropathy (OIPN)

Oxaliplatin, a third generation platinum-based agent, is the principal chemotherapy agent for the treatment of colorectal cancer (CRC) and has significantly improved the treatment and overall survival rates of patients [1–4]. CRC is the third most commonly diagnosed cancer in men and women, with over 134,000 new cases of CRC expected to be diagnosed in 2016.[5,6]. Oxaliplatin is also used for the treatment of pancreatic, gastric, esophageal, lung, ovarian and breast cancers [7–10]. Depending on the cancer stage, up to 80% of people with CRC receive chemotherapy as part of their treatment [6].

Despite its effectiveness, the peripheral neuropathy caused by oxaliplatin therapy remains the major treatment-limiting factor [11,12] . Symptoms of oxaliplatin-induced peripheral neuropathy (OIPN) often have debilitating and sometimes disabling consequences such as cold intolerance, changes in sensation of the extremities, and functional impairments which limit mobility, activities of daily living and self-care. These functional limitations compromise safety, the ability to continue work, and quality of life (QoL) [13–16]. In some cases, OIPN may cause prolongation of oxaliplatin administration times, dose reductions, treatment delays, or discontinuation to avoid irreversible sensory nerve damage [16–18].

There is no effective OIPN prevention method, and pharmacologic management is suboptimal [19,20]. Approaches to OIPN prevention such as calcium/magnesium (Ca/Mg) infusions, the slow infusion of oxaliplatin and the stop-and-go approach, in which

oxaliplatin infusion is temporarily suspended and reintroduced at a later point during treatment, have been ineffective in preventing OIPN [21–24]. Pharmacologic management of OIPN with duloxetine shows promise but is associated with side effects, such as dizziness, nausea, restlessness, somnolence and urinary hesitancy [19,25,26].

OIPN differs from CIPN caused by other chemotherapy drugs, mainly because of symptoms presentation. Acute OIPN (a-OIPN) consists of symptoms that appear during each treatment cycle, and may not completely subside before the next infusion [14,27,28]. Dose-dependent OIPN (d-OIPN) is the phenomenon of increased severity and persistence of symptoms as the total dose of oxaliplatin increases with repeated cycles. Oftentimes those with d-OIPN experience chronic OIPN (c-OIPN) which is persistence of d-OIPN symptoms following treatment cessation [29–31]. Although these symptom phases are distinct from each other, they are not independent of each other. In fact, the severity of a-OIPN symptoms has been shown to predict the severity of c-OIPN symptoms [27,32–34]. Symptoms that characterize OIPN phases are presented in Table 1.

1.2. Incidence and Prevalence of OIPN

It is estimated that approximately 65,280 and 27,200 individuals will develop d-OIPN and c-OIPN, respectively, in 2016. D-OIPN prevalence estimate for 2014 is 72.3%, based on a 12-study subset analysis of CIPN data from a systematic review and meta-analysis [35]. OIPN incidence rates are summarized in Table 1.

Estimating the prevalence and incidence of OIPN is challenging for several reasons, including variation in measurement of the phenomenon. For instance, some report OIPN incidence rates using common toxicity criteria (CTC) clinical grading scales (e.g. NCI-CTC) [36,37], while others estimate OIPN incidence based on severity of specific

Table 1: Summary of characteristics of OIPN

Characteristics	Acute OIPN (a-OIPN)	Cumulative dose-dependent OIPN (d-OIPN)	Chronic OIPN (c-OIPN)
Onset of symptoms [1,14,28,33,38]	Usually during infusion or immediately after.	After mean cumulative dose > 500mg/m2. Some patients may experience the onset sooner.	Symptoms follow d-OIPN
Duration of symptoms [16,39]	Transient in nature. Peaks in 3 days. Lasts for up to 7 days.	Persistent in nature. Lasts from onset through duration of treatment.	Symptoms during this phase are persistent and long term in nature. They can last for > 2 years after treatment completion.
Incidence rates [14,16,18,28,33,36,37]	75% – 95% Symptom severity is determined by number of symptoms present. Median number of symptoms is 4	Grade 1 = 45% - 48% Grade 2 = 28% - 32% Grade 3 = 12% - 13%	Grade 1 = 20% Grade 2 = 3.5 Grade 3 = 0.5%
Do symptoms improve? [14,16]	Yes. There is partial and in some cases, complete resolution between treatment cycles.	No. Symptoms may remain stable, but usually gets worse as treatment progresses and cumulative dose increases	Maybe. Symptoms may become worse after treatment completion ("coasting") and complete symptom resolution is not common.
Associated symptoms [14,16,18,29,32]	Throat discomfort, muscle cramps, pharyngolaryngeal dysesthesias, jaw stiffness, breathing and swallowing difficulties, electric shocks, voice changes, perioral dysesthesia, laryngospams	Dysesthesias, paresthesias and hypoesthesias in the fingers and feet presenting in stocking glove fashion. Symptoms in hands > feet. Proprioception loss, motor weakness, gait disturbances, decreased deep tendon reflexes	Same as d-OIPN. Symptoms in feet > hands.
Risk Factors [30,40–44]	Sub-clinical neuropathy	Increased cumulative oxaliplatin dose, greater number of treatment cycles, severity of a-OIPN, male gender, increased BMI, increased magnesium, anemia	Increased total cumulative dose, greater number of treatment cycles, severity of a-OIPN, Alcohol use.

neuropathy symptoms (e.g. numbness and tingling) assessed with patient-reported questionnaires (PRQs) [14,15]. Agreement on the incidence rates and severity of symptoms vary between the CTC grading scale and PRQs [45,46]. For example, agreement between the Numeric Analogue scale (NAS), a self-report measure, and NCI-CTC grade for OIPN presence was 65% [45]. This suggests that self-report and clinical grading scales cannot be used interchangeably to evaluate incidence rates or severity of OIPN.

1.3. Pathophysiology associated with OIPN development

Although the pathophysiology of OIPN is not fully understood, small sensory nerve fiber degradation and loss of intra-epidermal nerve fiber density (IENFD) do occur [14,47,48]. Processes which may contribute to small fiber degradation include damage to sensory fiber dorsal root ganglion (DRG) [49–51], ion channel dysfunction [49,52–55], damage to mitochondrial DNA [56] and oxidative stress [57–59].

Since effective preventive measures for OIPN do not currently exist and treatment remains suboptimal, improved documentation of nerve fiber function during oxaliplatin treatment may lead to earlier and more accurate OIPN diagnosis, which may better inform the timing of interventions and therapeutic trials to treat OIPN.

1.4. OIPN-associated Neuropathic Pain (OIPN-NP)

Neuropathic pain (NP) results from a primary lesion or disease affecting the somatosensory system [60,61]. OIPN is commonly associated with NP, which may develop early during treatment, become progressively worse as treatment progresses, and persist following treatment completion [14,26,44,62–65]. OIPN-NP is difficult to manage, and can have similar debilitating consequences as OIPN, based on findings from studies examining both [13,14,66]. Not all patients with OIPN develop NP. Estimates from small

studies indicate that approximately 13% - 38% of patients experience NP with oxaliplatin treatment [62,65,67].

Patients who develop OIPN-NP have described it as "shooting", "burning", and "piercing" [63,64,68]. Some studies have demonstrated the involvement of small myelinated Aδ and unmyelinated C fibers in OIPN-NP [16,62,63,67]. However, clarification of (1) the temporal relationship between OIPN and associated NP; and (2) the relationship between OIPN-NP and QoL is needed, to better understand this phenomenon and its effects on patients' QoL. This information may improve diagnosis and management of OIPN-NP.

1.5. Quality of Life (QoL) and its association with OIPN-NP and OIPN

Quality of life (QoL) is an important endpoint in the management of cancer and can be defined as an individual's perception about their health status [69]. QoL is often used interchangeably with terms like health status and functional status to describe overall health and the impact of disease and treatment on individuals [70–72]. It is also used to characterize functional ability, including physical functioning, social functioning, and role-functioning. OIPN is negatively associated with QoL[13–15,65,66] such that QoL worsens with increasing OIPN symptoms and duration. Two studies demonstrated that OIPN-NP was associated with a decrease in QoL [15,66]. It is important, therefore, to be able to distinguish between OIPN and NP and the influence of each on QoL outcomes. This may inform and help guide interventions during chemotherapy treatment that may allow patients to maximize QoL.

1.6. Assessment of OIPN

1.6.1. Clinical Scales

The best method for accurately assessing the presence, severity and progression of any form of CIPN remains a matter of debate and discussion [73–77]. Currently, several methods are used to assess OIPN in the clinical setting. Severity of OIPN is most commonly assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTC), a clinical grading scale [78]. The NCI-CTC assesses signs and symptoms of CIPN and its effect on daily functioning [77,79]. Patient-reported questionnaires (PRQs) are another type of clinical scale used to assess OIPN in the clinical setting. The PRQs frequently used, assess the effect of OIPN on QoL as an indirect measure of OIPN severity. [14,65,80,81]. At least six oxaliplatin-specific clinical grading scales and four oxaliplatin-specific PRQs have been developed and used for the assessment of OIPN [78]. Composite scales such as the Total Neuropathy Score (TNS©) are also used to assess OIPN. Composite scales include self-report items and clinician administered testing. TNS© incorporates self-report items; physical examination, including quantitative sensory tests like vibration perception and pin sense; and nerve conduction study (NCS) results into a single measure, which can be administered by a neurologist [68,82,83]. A simplified clinical version of the TNS© (TNS-clinical (TNSc©)) which excludes NCS is appropriate for use by non-neurologists.

Clinical grading scales and PRQs are quick and easy to administer. They are designed to provide a rapid evaluation for clinical trials and are most useful in screening patients and providing an overall clinical picture of peripheral neuropathy [73,76,77,83]. Composite scale like the TNS© are more precise, can discriminate between different

forms of sensory deficits and is able to provide discrete anatomical locations from where the symptoms of CIPN are originating [77,84].

Clinical scales however, come with some important limitations. Although clinical grading scales and PRQs are easy to administer and are commonly used, they do not assess sensory nerve fibers, which could offer insight into the pathophysiology of OIPN [76,77,83]. Also, whereas PRQs have strong psychometric properties, weak to moderate inter-rater agreement has been reported for the NCI-CTC and poses a hindrance to score interpretation. [73,75]. Finally, the TNS© is time-consuming to administer, requires examiner training, specialized equipment and is not available to all providers [76,77,83,84]. The simplified TNSc© remains time consuming to administer and requires specialized training before appropriate use [76,84].

1.6.2. Nerve conduction studies (NCS) and quantitative sensory testing (QST)

Nerve conduction studies (NCS) and quantitative sensory testing (QST) have been used to characterize sensory fiber function in patients with OIPN [16,47,62,63,85–89]. NCS evaluate the electrical conduction of peripheral nerves by measuring the speed at which impulses travel through the nerves. QST uses psychophysical tests to assess somatosensory functions by measuring responses to calibrated stimuli [90,91]. These tests include cold detection threshold (CDT), warm detection threshold (WDT), heat pain threshold (HPT), cold pain threshold, mechanical detection threshold (MDT), vibration detection threshold (VPT), and pin sense (sharp-dull discrimination). These tests are discussed in detail in Chapter 2. Although NCS studies are sometimes used for additional evaluation of OIPN, poor sensitivity to small fiber neuropathy has been noted [48,92]. In

fact, as many as half of patients with CIPN have normal NCS [48,93]. Therefore, it may not be useful for diagnosis of OIPN [48].

Compared to NCS, QST is more sensitive to small fiber neuropathy [48]. QST in patients with OIPN reveals abnormal cold, warm, vibration and mechanical detection thresholds [48]. QST is a reliable and accurate measure of OIPN and some tests like pin sense and VPT are used in the clinical setting for CIPN evaluation [94–96]. Because it is a psychophysical assessment, QST results can be influenced by noise, ambient temperature, and concentration of the person being assessed [97]. Since QST is more sensitive to changes in small fiber activity and NCS to changes in large fiber activity, when used together, QST and NCS can improve the accuracy of CIPN diagnosis by up to 95%, compared to QST or NCS alone [48,67]. However, QST and NCS tests are not practical for use in the clinical setting because they require considerable time, specialized equipment and tester training to accurately conduct these tests. In the case of QST, standardized series of instructions, which the patient may not be able to understand and properly follow, are required to properly perform the assessment. NCS can also be uncomfortable and the results require the expertise of a neurologist for interpretation.

1.6.3. Current perception threshold (CPT)

Current perception threshold (CPT) uses sine-wave current electrical stimulus delivered at specific frequencies to elicit responses from the peripheral nerves. The absolute value of the lowest perceptible current is determined to be the perception threshold. [98,99]. Since other nerve fibers are typically in their refractory periods at the wavelength in which a particular nerve fiber is depolarized, neuroselectivity for large Aβ and small Aδ and C fibers are achieved by applying sinusoidal waves at selected pre-

determined wavelengths of 2000Hz, 250Hz and 5Hz, respectively[100–103]. CPT is easier to administer than NCS and QST studies, and interpretation of results is simpler than for NCS. Unlike QST, normative values are available when interpreting CPT results.

CPT is a promising approach for characterizing OIPN because it has the capability to assess small and large sensory fibers. For this reason, like QST and NCS combined, it may possess a high diagnostic accuracy for OIPN and may improve early detection and monitoring of OIPN in addition to providing insights about sensory fiber changes that produce OIPN over time. CPT has been used in the clinical setting to assess peripheral neuropathy in diabetes [98,104–109] and carpal tunnel syndrome [110,111]. Although CPT has been used previously in the setting of CIPN, data on its performance relative to CIPN grading scales and QST is limited [43,112].

1.7. Problem statement, study purpose, and specific aims

OIPN and OIPN-NP are serious problems with disabling consequences for many patients. Lack of routine measurement of sensory fiber function hinders understanding of the pathophysiology of OIPN and curtails development of effective management strategies. Also lacking is information about how OIPN-NP influences QoL.

The purpose of this study, therefore, is to explore the role of CPT in assessing OIPN, describe characteristics of OIPN-NP and its relationship with OIPN, and characterize the relationship between OIPN-NP and QoL in patients receiving oxaliplatin-based chemotherapy. Study aims include:

Aim 1: To evaluate CPT for the assessment of sensory fiber function in patients who develop d-OIPN after receiving oxaliplatin for treatment of gastrointestinal cancers. Specifically, to:

1a. Describe the associations between CPT (5Hz, 250Hz, and 2000 Hz) and QST (vibration perception, pin sense, warm detection, cold detection and mechanical detection thresholds).

1b. Determine if CPT (5Hz, 250Hz, 2000 Hz) varies by d-OIPN (NCI-CTC) status.

Aim 2: To describe the relationship between OIPN-NP and d-OIPN and determine their impact on quality of life (QoL) in patients who received oxaliplatin for gastrointestinal cancers. Specifically, to

2a. Describe the progression of OIPN-NP (NPS, cold pain and heat pain thresholds) over the course of oxaliplatin treatment.

2b. Explore the association between OIPN-NP (NPS, cold pain, and heat pain thresholds) and d-OIPN (NCI-CTC).

2c. Determine if OIPN-NP (NPS, cold pain and heat pain thresholds) and d-OIPN (NCI-CTC) have independent associations with QoL.

It is hypothesized that CPT 2000Hz, 250Hz and 5Hz will be associated with QST measures of the respective sensory fibers they assess. Further, OIPN and OIPN-NP will be inversely associated with QoL of patients receiving oxaliplatin-based chemotherapy.

1.8. Theoretical Framework

The Neuromatrix Theory of Pain (TNTP) will provide the organizing framework for this study [113,114]. This theory explains how the body generates sensations of pain and its accompanying physiological responses as well as how inputs into the body may influence the generation and perception of pain.

1.9. Significance of study

This study is significant because it evaluates CPT, a promising method for measuring OIPN in which sensory fibers can be assessed easily and quickly. The assessment of sensory fiber function is important because it may provide some insight into the pathophysiology of OIPN and could provide better monitoring of OIPN onset and progression compared to what is now available in the clinical setting. Findings from this study will provide a foundation for future investigation of CPT responsiveness to change in OIPN severity. It will also provide feasibility information for evaluating the use of CPT with chemotherapy agents other than oxaliplatin.

A better understanding of the relationship between OIPN and OIPN-NP will inform onset of OIPN-NP. In addition, understanding the characteristics of OIPN-NP may provide researchers with information that may enhance efforts to manage OIPN-NP, which may lead to improvement in the QoL of patients.

CHAPTER 2

THEORETICAL FRAMEWORK AND REVIEW OF LITERATURE

2.1. Theoretical framework

2.1.1 Theory Selection

The theoretical framework of this study is organized using the Neuromatrix Theory of Pain (TNTP). This study aims to provide evidence of CPT construct validity in the setting of OIPN. TNTP was selected for use for this study because it provides a framework for understanding the influence of oxaliplatin on sensory nerve fibers through examination of the relationship between CPT and clinical measures of OIPN. TNTP also provides a framework for understanding the relationship between OIPN, OIPN-NP and QoL.

2.1.2. The Neuromatrix Theory of Pain (TNTP).

TNTP addresses the concept, causes, and influences of pain [113–116]. The central concept of this theory is the body-self neuromatrix, described as a large network of neurons that connect the cerebral cortex to both the thalamus and the limbic system. This network has a spatial distribution as well as synaptic links that are genetically determined and refined by sensory inputs [113]. Two key attributes arise from this concept. The first attribute is the sentinet hub, which describes areas of the brain where the stream of nerve impulses is concurrently converted to both awareness (e.g. that the top of the stove is hot) and movement patterns aimed at achieving specific goals (e.g. removing the hand from a hot stovetop). The second attribute is the neurosignature, described as the characteristic response pattern imparted on the neuromatrix, by repeated cyclical processing and synthesis of nerve impulses. The neurosignature is a continuous outflow from the body-

self neuromatrix and consists of 'pre-programmed' output response actions such as pain perception, stress regulation and voluntary/involuntary actions taken to evade pain. [115]. Thus, the theory proposes that the pain experience is a predetermined output neurosignature, produced by genetic and sensory influences in the body-self neuromatrix. This experience can be modulated by sensory and cognitive events, which may produce lesions in the muscles, bones and nerves. These lesions may in turn, alter the patterns of the neurosignature in such a manner as to give rise to chronic pain [114].

2.1.3. Theory Summary

Under normal circumstances, the pain experience consists of pre-determined responses (or neurosignatures), which include our perception of pain (e.g. severity and location) our reaction to pain (including voluntary and involuntary actions) and stress regulation programs (such as increased cortisol and endorphin levels). These responses are created by a process of cyclical processing and synthesis of cognitive inputs such as past experiences, physiological inputs from sensory signaling systems and inputs from parts of the brain responsible for homeostasis and stress regulation. This process is guided by both genetics and a balanced stress-regulatory system to form the entire body-self neuromatrix [113]. The neuromatrix, therefore, is a sum of these various neurosignatures. The development and maintenance of these neurosignatures are influenced by the inputs into the neuromatrix. Loss of regulatory control or new sensory inputs leads to new cyclical processing and synthesis, which results in new neurosignatures. Depending on which part of the neuromatrix is affected by this regulatory loss or depending on the nature of the new sensory input into the neuromatrix, chronic pain may be the result [113]. The body-self neuromatrix is central to the theory and

provides context for the proposed study, since the constructs being assessed (OIPN and NP) are considered neurosignatures emanating from the body-self neuromatrix due to the influence of oxaliplatin on sensory signaling systems.

2.1.4. Conceptual relevance of TNTP to proposed study

Oxaliplatin influences peripheral sensory input to the central nervous system by inducing sensory and morphological changes to sensory nerve fibers and altering their normal function, resulting in sensory neuropathy and NP. The persistence of d-OIPN and NP following cessation of oxaliplatin suggests that oxaliplatin-induced changes to sensory fiber function and therefore sensory input into the body-self neuromatrix have resulted in the creation of a new neurosignature pattern, which is responsible for the persistence of c-OIPN and NP. TNTP provides an appropriate framework for studying how oxaliplatin may alter sensory fiber function (measured by CPT) and its input into the body-self neuromatrix to produce OIPN (measured by CTC) and NP (measured by NPS and QST) experienced by individuals receiving oxaliplatin.

2.1.5. Adaptation of TNTP and Conceptual framework for the study

Based on the variables available for use from the primary study, several constructs of TNTP were examined. Input constructs such as cognitive inputs (e.g. previous experience with oxaliplatin, OIPN and NP) were not addressed because participants were chemotherapy naive. Emotion-related inputs (e.g. stress levels associated with cancer diagnosis and chemotherapy treatment) were not assessed in the primary study and were not available for inclusion in the conceptual framework of the study. Also, output constructs such as action program outputs (e.g. pain behavior patterns) and stress regulation outputs (e.g. cortisol and endorphin levels) were not

assessed in the primary study and as such were not included in the present study's conceptual framework. The following constructs from TNTP were used to generate the conceptual framework for this study (See Figure 1).

Inputs to neuromatrix that were examined include peripheral afferent sensory fiber function assessed by QST and CPT, which served as sensory signaling input into the body-self neuromatrix. Outputs from neuromatrix that were examined included NP, assessed by the NPS and QST (heat and cold pain thresholds), OIPN assessed with the NCI-CTC scale, and QoL assessed with the FACT/GOG-Ntx.

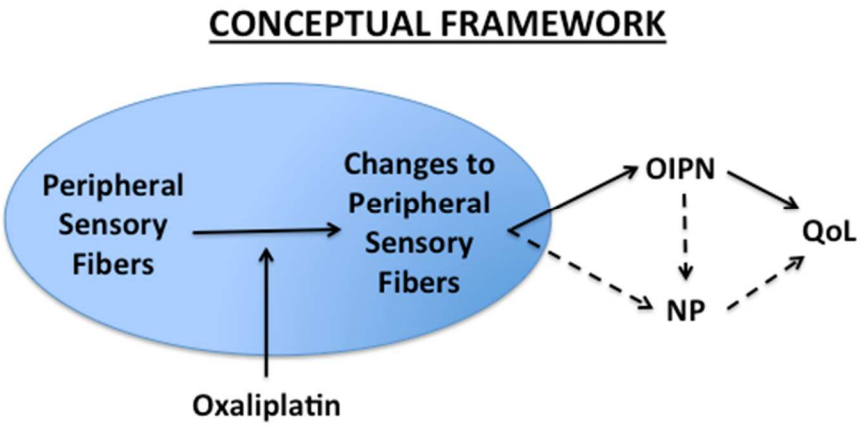


Figure 1: Conceptual framework of proposed study

2.2. Review of the scientific literature

2.2.1. Introduction

Oxaliplatin produces its antineoplastic effects mainly by forming platinum adducts with DNA, thereby hindering DNA transcription and replication resulting in cell death [117–121]. Oxaliplatin and its metabolites damage peripheral sensory nerves, which eventually leads to OIPN symptoms. This chapter will provide a literature synthesis of the effects of oxaliplatin on peripheral sensory nerves and the clinical manifestations of

these effects. The relationships between OIPN, OIPN-NP, and QOL will also be discussed, with an emphasis on measures used in this study.

2.2.2. Clinical presentation of OIPN

The clinical course of OIPN is well described [14,18,32,122]. In a randomized control trial (n = 346) of OIPN prevention and a prospective, longitudinal study examining the relative toxicity profile of oxaliplatin regimens (n = 170), over 85% of participants developed a-OIPN symptoms, primarily during the first cycle of oxaliplatin [14,27]. OIPN symptoms reported by patients during the acute phase include throat discomfort, muscle cramps, pharyngeal dysesthesias, cold sensitivities as well as breathing and swallowing difficulties [14,27,44]. Up to 30% of patients with OIPN receive reduced doses or discontinue oxaliplatin treatment due to severity of a-OIPN symptoms [16,32,44].

The cumulative dose-dependent phase of OIPN (d-OIPN) is characterized mainly by sensory deficits. Paresthesias or numbness and tingling are the most commonly reported symptoms of d-OIPN, are more severe in the hands than the feet and are often accompanied by loss of proprioception [14,29,65]. Autonomic and motor deficits such as motor weakness, gait disturbances, and loss of deep tendon reflexes have also been reported but are less common [14,29,47,63]. Onset of d-OIPN usually occurs after patients receive a cumulative dose of 500mg/m2 of oxaliplatin, although symptoms have been reported earlier [62]. Severity of d-OIPN symptoms is also associated with the number and severity of a-OIPN symptoms [14,32,44]. During d-OIPN phase, symptoms become progressively worse with increasing cumulative doses, sometimes requiring increased duration of infusion times, decrease in oxaliplatin dose or discontinuation of oxaliplatin [44]. Median recovery time for d-OIPN is about 13 weeks after treatment ends [123]. However

at doses >1000mg/m^2 these symptoms may be irreversible, leading to c-OIPN [124]. Most patients who complete the entire course of oxaliplatin treatment receive on average between 770mg/m^2 to 1020mg/m^2 of oxaliplatin [27,44,62].

Chronic OIPN (c-OIPN) occurs when symptoms persist at least several months after oxaliplatin treatment has ended. In some studies, participants are considered to have c-OIPN when symptoms persist beyond 3 months after treatment completion, while in others, participants are considered to have c-OIPN when symptoms persist for 6 or more months after treatment completion [14,47,62]. Once established, c-OIPN symptoms can persist for 18 months and up to 11 years after treatment completion [14,29,125,126]. Symptoms reported during c-OIPN are the same as those present during d-OIPN, the most common being numbness and tingling [65]. In contrast to d-OIPN, symptoms of c-OIPN are more severe in the feet than the hands. Symptom intensity may decrease over time, but in many cases, complete recovery does not occur [13,14,29,44,62]. Some functional consequences of c-OIPN include reduced dexterity, such as difficulty manipulating small objects and limitations in mobility, like difficulty walking due to solar numbness [13,14].

2.2.3. Somatosensory and electrophysiological changes associated with OIPN

Several somatosensory and electrophysiological changes correspond with the clinical symptoms of OIPN. These changes provide insight into the effects of oxaliplatin on peripheral sensory nerves and are summarized in Table 2. External stimuli activate receptors on peripheral afferent fibers (PAFs), primarily the large and myelinated Aβ and Aδ fibers as well as the small, unmyelinated C fibers of the somatosensory system. Receptors convert these stimuli into action potentials (APs) which are transmitted by the PAFs, through the spinal cord to the brain. The electrical activity generated by these APs

can also be measured using nerve conduction studies, which determine the amplitude and speed with which the APs travel through the PAFs.

A-OIPN is characterized by cold hypersensitivies, dysesthesias (i.e. unpleasant, abnormal sense of touch), and in some cases pain, especially when touching cold objects [27,44]. These symptoms are significantly correlated with impaired cold and heat detection thresholds mediated by Aδ and C fibers respectively. Additionally, changes in cutaneous sensation or mechanical detection threshold (MDT) and vibration perception mediated by Aβ fibers are associated with a-OIPN symptoms [16,44]. Patients who experience a-OIPN have decreased cutaneous sensation, vibration perception, and increased cold pain threshold (See Table 2). Although a-OIPN is not the focus of this study, the somatosensory changes that occur during a-OIPN have been shown to predict the presence of grade 2 and 3 d-OIPN 1 year after treatment initiation. [44]

As treatment progresses, the onset of d-OIPN symptoms is characterized by dysesthesias, paresthesias and proprioception loss. These symptoms are associated with somatosensory changes such as decreased proprioception, mechanical detection, and vibration detection thresholds, mediated by Aβ sensory fibers [29,44,47]. Changes such as increased warm detection and cold pain thresholds mediated by C-fibers have also been associated with the development of d-OIPN. [44,62,127]. Somatosensory changes associated with c-OIPN symptoms are similar to those observed in d-OIPN but also include decreased ability to detect sharp sensation and decreased cold detection threshold, which are mediated by Aδ fibers [13,16,47,62].

In summary, all 3 peripheral sensory fiber types are affected to some degree over the course of oxaliplatin treatment. However, Aβ- and C-fiber somatosensory modalities

are the most affected during d-OIPN, suggesting that these two sensory fibers are primarily affected during d-OIPN [13,16,44,47,48,62,63]. Electrophysiological studies on the other hand show that OIPN is associated with decreased sensory action potential (a-SAP) amplitude [29,32,47].

Table 2: Effects of OIPN on peripheral sensory nerves

Test	a-OIPN	d-OIPN	c-OIPN
IENFD [47,48]	N/A	Decreased IENFD [47]	Decreased IENFD [47,48]
Somatosensory profile	Decreased VPT (Aβ) [16,62] Increased cold pain threshold (C) [16,62] Decreased HPT (C) [16,62] Increased WDT (C) [44,62] Decreased Bumps Score (Aβ) [62] Increased MDT (Aβ) [44] Increased CDT (Aδ) [44]	Decreased VPT (Aβ) [29,47,62] Increased cold pain threshold (C) [44,62,63] Increased WDT (C) [62,63] Decreased pin sense (sharpness) (Aδ) [47] Decreased proprioception (Aβ) [29] Increased MDT (Aβ) [44]	Decreased VPT (Aβ) [13,16,47] Decreased pin sense (sharpness) (Aδ) [13,16,47] Decreased proprioception (Aβ) [16,29] Decreased Bump score (Aβ) [62] Decreased CDT (Aδ) [62] Increased WDT (C) [62] Decreased cold pain threshold (C) [62]
Nerve conduction studies	Decreased amplitude of sensory action potential (a-SAP) [47]	Decreased amplitude of sensory action potential (a-SAP) [18,29,32,47,122]	Decreased a-SAP [13,29,32,47,48,122] Decreased amplitude of compound motor action potential (a-CMAP) [48]
Sensory fibers affected	Predominantly Aβ and C fibers	Predominantly Aβ and C fibers	Predominantly Aβ and C fibers

2.2.4. Mechanisms associated with the development of OIPN

Although the pathophysiology of OIPN is not yet fully understood, some mechanisms which contribute to the phenomenon have been identified. Peripherally, oxaliplatin and its metabolite oxalate alter calcium signaling of sensory neurons on

peripheral afferent fibers (PAFs), leading to the influx of calcium ions through the L-type calcium channels [128,129]. Oxaliplatin and oxalate also directly activate TRPA1 receptors on PAFs [53,130–132]; enhance the activity of voltage-gated sodium channels [128,129,133–135] and suppress potassium channel activity [133,136–139] on PAFs. These processes lead to a hyper-excitable neuronal state, which contributes to the development of cold sensitivity and pain. Since oxaliplatin is typically administered every 2 to 3 weeks for a period of at least six months the frequent administration and subsequent production of oxaliplatin metabolites contribute to ion channel dysfunction [139]. These changes coupled with activation of thermoponsive nociceptors by cold temperatures inevitably lead to peripheral sensitization or an increase in responsiveness of nerve fibers to noxious stimuli and/or nociceptive mediators, and a constant generation of action potentials (APs) [140]. In other words, sensory nerve fibers become hypersensitive to cold temperatures, leading to sensitivity and/or a painful experience. This series of events also explains the symptoms of cold sensitivity and cold pain experienced during a-OIPN [52,131,139].

There is increasing evidence suggesting that accumulation of oxaliplatin in the dorsal root ganglion (DRG) of neurons, damage to the DRG, and inflammation play important roles in the development of d-OIPN and c-OIPN [50,51,59,141,142]. Rodent models of OIPN demonstrate that oxaliplatin causes degeneration of DRG cells and axons, impairs neuronal transport and alters proper ion channel functioning of affected neurons [51,137,143]. In patients with d-OIPN and c-OIPN, long-term morphological changes in sensory fibers, including loss of intra-epidermal nerve fibers (IENFD) have been reported [47,48].

2.2.5 OIPN-associated NP (OIPN-NP)

Neuropathic pain (NP), a major problem associated with OIPN , is caused by damage to nerves, particularly peripheral afferent fibers (PAFs) [16,25,26,48,63,140,144]. OIPN-associated NP (OIPN-NP) differs from OIPN in symptom presentation and somatosensory profile. The characteristics of OIPN-NP and how it differs from OIPN are summarized in Table 3. Damage to C fibers contribute to the development of OIPN and OIPN-NP. However, an important distinction between OIPN and OIPN-NP is that whereas damage to Aβ fibers contribute to OIPN, damage to Aδ fibers contribute to the development of OIPN-NP symptoms. Another distinction is that the intensity of OIPN-NP tends to remain the same or worsen after oxaliplatin treatment is completed, while OIPN symptoms may improve after treatment completion in some cases [13,14,44,62,66].

OIPN-NP may be present during a-OIPN [23,25,56,72], d-OIPN and or c-OIPN [14,29,44,63]. Results from a longitudinal study (n = 78) demonstrated that OIPN-NP (increased cold pain thresholds) began at cumulative doses of 115mg – 345mg, which is lower than the average d-OIPN onset of 500 mg/m^2 and worsened progressively with increasing doses of oxaliplatin. Although NP improved over time among the participants, 20% of those who experienced NP during treatment, continued to be affected six months after oxaliplatin was discontinued [62]. Similar results have been reported in other studies. [16,127]

In a longitudinal study (n = 30) examining the predictors of d-OIPN, those who developed d-OIPN reported OIPN-NP within an hour of the first oxaliplatin infusion cycle, compared to those who did not (mean BPI score = 1.5, p = 0.011). OIPN-NP

persisted throughout the first treatment cycle and increased in intensity with subsequent treatment cycles [44].

Table 3: d-OIPN and OIPN-NP: similarities and differences

	d-OIPN	OIPN-associated NP
Nature of symptoms	Mainly sensory deficits and to a lesser extent, motor and autonomic deficits [14]	Purely sensory in nature
Clinical presentation [145,146]	Include "gain of function" and "loss of function" deficits. Characterized mainly by paresthesias and dysesthesias. See Table 1 for details	Include only "gain of function" deficits. Characterized by hyper-sensitivities to noxious and non-noxious stimuli
Description of symptoms	Primarily described as "numbness" and "tingling". Most present in hands and feet. Symptoms progress proximally in a "stocking glove" manner. See Table 1	Described as "sharp", "dull", "intense", "unpleasant", "heavy", "shooting", "burning". Symptoms remain mainly in the finger tips and sole of the feet. There is no progression pattern associated with this condition
Sensory fibers affected	Primarily large Aβ and small unmyelinated C fibers.	Primarily small unmyelinated C fibers, but may also affect myelinated Aδ fibers.
Somatosensory profile [145,146]	Decreased VPT (Aβ) [29,47,62], Increased cold pain threshold (C) [44,62,63], Decreased HDT (C) [62,63], Decreased pin sense (sharpness) (Aδ) [47] Decreased proprioception (Aβ) [29] Increased MDT (Aβ) [44]	Increased cold pain and decreased mechanical pain thresholds [62].
Onset/Duration of symptoms	Onset occurs after receiving a mean dose of about 500mg/m2 of oxaliplatin. Symptoms persist/worsen during treatment and may/may not improve after treatment stops	Onset occurs at the beginning of oxaliplatin treatment. In some cases, during the first cycle of oxaliplatin infusion. Symptoms persist/worsen during treatment and often continues to worsen after treatment stops
Mechanism	Mechanism responsible for development to d-OIPN is not fully understood. Damage to and degeneration of DRG neurons due to oxidative stress and accumulation of oxaliplatin in DRG neurons have been shown in rodent models to contribute to the development of OIPN	Ion channel dysfunction caused by oxaliplatin and its metabolites sensitize peripheral nerves to cause cold sensitivity and cold-associated pain. Sensitization of WDR in DH due to peripheral sensitization is thought to contribute to the maintenance of NP.

In a secondary analysis of data from an OIPN prevention trial (n=353) where 89% of the participants developed d-OIPN, OIPN-NP, along with numbness and tingling were

the most highly rated symptoms of d-OIPN. Further, while symptoms of numbness and tingling improved 3 months after treatment completion, OIPN-NP persisted and became worse during the same period [14]. In this study, OIPN-NP intensity remained the same or worse 18 months after oxaliplatin treatment was completed.

2.2.6. Mechanisms associated with the development of OIPN-NP

NP associated with d-OIPN appears to result from mechanisms other than those that drive d-OIPN alone. Whereas loss of IENFD and accumulation of oxaliplatin in DRG of peripheral sensory fibers play important roles in the development of d-OIPN, the sensitization of dorsal horn (DH) neurons (central sensitization) resulting from prolonged AP generation by PAF has been suggested as a potential mechanism for development of oxaliplatin-associated NP [127,144]. The DH is located in the posterior segment of the spinal cord and contains three main types of neurons i.e. nociceptive-specific, wide dynamic range (WDR), and non-nociceptive neurons [147–149]. The DH is responsible for receipt and transmission of sensory stimuli from the body to the brain (e.g. touch, vibration and pain). This concept of DH sensitization is supported by increases in WDR neuronal activity, which corresponds with the development of mechanical allodynia or painful response to otherwise non-painful stimuli, and cold hyperalgesia in mice model of OIPN [150].

2.2.7. Influence of OIPN and NP on QoL

QoL is a complex entity comprising a number of components including physical functioning, health status, life conditions, symptoms and satisfaction with life among others [151]. In oncology, QoL includes concepts of physical and mental health, physical and role functioning, well-being and perception of overall health [80,152–155]. HRQoL is

defined as the extent to which a medical condition and/or its treatment affects the usual or expected emotional, social and physical well-being of the individual [156]. HRQoL is used to describe the perceived health of individuals or their experiences as they relate to health, disease, impairment and disability [157,158]. HRQoL incorporates aspects of life other than health (e.g. income, environment, etc.) which influence health and therefore QoL [72].

OIPN negatively affects QoL[13–15,65,66,159,160]. A retrospective cross sectional study (n = 128) demonstrated an inverse association between OIPN severity and HRQoL across all domains of HRQoL (physical functioning, $r = -0.22$, $p<0.05$; emotional role, $r=-0.36$, $p=0.01$; physical role, $r = -0.32$, $p<0.01$; bodily pain, $r = -0.36$, $p<0.001$; vitality, $r = -0.23$, $p<0.05$; general health, $r = -0.003$; mental health, $r = -0.26$, $p<0.05$; social functioning, $r = -0.36$, $p<0.001$) [15]. In a population-based cross-sectional study of CRC survivors who received chemotherapy only, surgery only, radiotherapy only or some combination of all three (n = 1643), participants who received oxaliplatin reported more OIPN which was associated with a larger decrease in HRQoL, compared to those who did not receive oxaliplatin (tingling, $\beta = 0.20$, $p < 0.001$; numbness, $\beta = 0.18$, $p < 0.001$; aching and burning pain, $\beta = 0.10$, $p < 0.001$) [65]. Similarly, in a randomized controlled trial of OIPN prevention (n = 347) participants reported OIPN symptoms of "numbness", "tingling" and "shooting and burning pain", the severity of which was inversely associated with QoL [14].

Hung et al [159] examined the influence of patient and clinical variables on HRQoL and symptom burden in CRC survivors (n = 134). Participants were examined at

diagnosis, 1 month- 3 months- and 6 months after diagnosis. All participants received surgery, chemotherapy and/or radiation. Pain at 1 month after diagnosis corresponded with decreased HRQoL. However, at 6-month post diagnosis, pain levels decreased in association with increased HRQoL. Quality of Life scores at 6 months were still lower than they were at baseline, reflecting an overall decrease in QoL during the 6-month period.

Two studies examined the relationships between OIPN-NP and QoL along the treatment trajectory. In a secondary analysis of a prospective longitudinal study (n = 3106), examining the association between OIPN-NP, QoL and clinician-reported difficulty in caring for patients with breast, lung, prostate or CRC, OIPN-NP was associated with deteriorating QoL among participants with CRC, but not among participants with other cancers. Further, CRC participants with higher levels of OIPN-NP at baseline experienced greater deterioration in QoL 28 – 35 days later, compared to those with lower levels of OIPN-NP at baseline [66]. A limitation of this analysis is that participants in the original study were heterogeneous in their cancer stages and were recruited at any point in their cancer trajectory. A greater percentage of participants in the CRC group had advanced stage disease, progressive disease (i.e. progression of cancer in spite of treatment), poorer performance status, > 5% body-weight loss within 6 months and poorer health, and were therefore sicker compared to participants in other cancer groups [161]. A cross-sectional study (n = 25), examining the late effects of OIPN was done using retrospective chart review, and 68% of the participants experienced OIPN-NP 24 months after treatment completion. Of these, 28% experienced functional impairments

related to OIPN-NP. Increased OIPN-NP severity and increased OIPN symptoms were associated with a decrease in functional QoL [13].

Because there is limited information available about the influence of OIPN-NP on QoL, further investigation is needed to understand the unique influence that OIPN and OIPN-NP have on QOL, which may allow better timing of interventions for NP along the treatment trajectory, which in turn, may impact QoL.

2.2.8. Assessment and monitoring of OIPN

Several methods are currently used to assess OIPN in the clinical and research settings. However, emphasis will be placed on instruments used in the current study.

a. Clinical grading scales

Currently, severity of OIPN is most commonly assessed using the NCI-CTC clinical grading scale [78]. The NCI-CTC scale assesses CIPN severity related to treatment toxicity [26,162]. The NCI-CTC scale was first developed in 1983 by the National Institutes of Health for the recognition and grading of adverse side effects of chemotherapy [41,163,164]. Adverse events are described as any new or undesirable event that may or may not be attributable to treatment [79,165]. The NCI-CTC grading scale is organized by body systems and uses a multimodal grading system to evaluate the acute and late effects of treatment regimens on cancer patients [164]. Thus, it can be used to assess adverse effects across the gastro-intestinal system, cardiovascular system, neurological system etc. Each scale grade (0 – 4) contains a list of symptoms, with lower scores describing mild symptoms while higher scores describe more severe symptoms. Inter-rater reliability of the NCI-CTC scale varies considerably [166,167]. In one study (n=37), NCI-CTC was reported to have a 45.9% inter-observer agreement across all grades of CIPN, a 42%

inter-observer agreement on grade 3 CIPN and an 81.1% inter-observer agreement on the distinction between grade lower or equal to grade 2 and grade 3 CIPN [75,166]. In a larger study (n = 281) in which rater training was conducted, inter-rater agreement was between 71% to 75% and intra-observer agreement was between 75% and 76% [167]. Consequently, the NCI-CTC can be a reliable measure to the extent that proper and consistent rater training is achieved. Finally, clinical grading scales like the NCI-CTC are designed for rapid evaluation of CIPN severity and are useful as screening tools [73,77]. The major weakness of this scale is that it cannot assess the involvement of specific components of the peripheral nervous system [79,164].

b. Patient-reported questionnaires (PRQs)

Patient-reported questionnaires (PRQs) are commonly used for OIPN assessment and consist of QoL questionnaires, which have been modified by adding specific items that address CIPN symptoms. They are commonly used in conjunction with the NCI-CTC grade scale to assess severity of CIPN [24,25,167]. PRQs are designed to evaluate the well-being of patients as well as the benefits and side effects of proposed or current treatment.

One of the PRQs commonly used to assess OIPN is the Functional Assessment of Cancer Treatment/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-Ntx) questionnaire [70,153]. The FACT/GOG-Ntx is a modified version of the Functional Assessment of Cancer Treatment – General (FACT-G), which was originally designed to assess QoL in cancer patients [70,153]. The FACT/GOG-Ntx is a 30-item questionnaire, which includes the four domains of the FACT-G: the 7-item Physical Wellbeing (PWB), the 7-item Social/Family Wellbeing (SFWB), the 6-item Emotional Wellbeing (EWB)

and the 7-item Functional Wellbeing (FWB) domains as well as an 11-item neurotoxicity (Ntx) subscale. Items on each domain are rated on a Likert scale of 0 – 5 with 0 being 'not at all' and 5 being 'very much'. Higher scores represent better QoL and lower severity of CIPN. The instrument also includes a computed subscale – the Trial Outcome Index –, which aggregates the PWB, FWB and Ntx domains to compute a functional subscale. The overall instrument is capable of capturing the impact of CIPN on QOL among patients receiving chemotherapy [153]. The FACT/GOG-Ntx has strong internal consistency (Cronbach's α of 0.84 - 0.9 at baseline and 0.94 - 0.74 after 12 months) in chemotherapy naïve patients [153]. The Ntx subscale has also been shown to be valid and responsive to change in the assessment of CIPN [153]. The instrument also showed a difference in scores in patients with CIPN over time, demonstrating responsiveness of the instrument to CIPN progression ($p = 0.017$) [153]. An oxaliplatin-specific Ntx subscale has been developed and validated for use in assessing OIPN [168].

Like the clinical grading scales, PRQs are quick and easy to use. Furthermore, PRQs possess strong psychometric properties. However, they do not assess sensory fiber degeneration and dysfunction. They are limited to patient perceptions of physical, psychological, and social consequences of CIPN and therefore are most useful at the patient care level. They do not provide additional insights into the pathophysiology of CIPN.

c. Quantitative sensory testing (QST)

Quantitative sensory testing (QST) includes a set of psychophysical assessments, which measures responses to calibrated, graded mechanical and thermal stimuli (innocuous and noxious), in order to quantify somatosensory functions [91,169]. They assess

the functional status of specific somatosensory modalities that function through the peripheral nervous system and central pain pathways [91]. Using parameters known to initiate various stimuli, QST employs techniques such as thermal (e.g. warm detection threshold and cold detection threshold), mechanical (e.g. von Frey filaments, pressure algometer, standardized brush) and vibratory thresholds (e.g. graded tuning fork), to assess specific sensory modalities as well as their corresponding PAFs and central pathways, by activating receptors on the endings of PAFs [170–173]. Mechanoresponsive Aβ fibers and their corresponding lemniscal pathway can be assessed through touch and vibration techniques such as the vibrometer, graduated tuning fork and calibrated von Frey filaments, while innocuous and noxious heat and cold are used to assess Aδ and C fibers and their corresponding spinothalamic pathway [170,174]. Increased detection threshold or inability to detect innocuous stimuli is indicative of decreased (hypoesthesia), or lack of sensitivity (anesthesia) of the affected nerve fiber. Decreased detection threshold for innocuous stimuli is indicative of increased sensitivity (hyperesthesia) of the nerve fibers. Increases in detection threshold of noxious cold stimuli, or decreases in detection thresholds for noxious heat stimuli are indicative of hyperalgesia (exaggerated response to painful stimuli) or allodynia (painful response to otherwise painless stimuli) and therefore decreased nerve function [91,175].

Since the entire somatosensory system can be assessed using QST techniques, it has been reliably used to describe loss of function (e.g. hypoesthesia and hypoalgesia) as well as gain of function (e.g. allodynia and hyperalgesia) in conditions such as OIPN [16,89]. Specific algorithms have been created for the delivery of stimuli and standardized instructions are given for subject responses [170,171,176]. Testing order is important because

many cutaneous fibers are polymodal in nature and can be activated by more than one mode of stimuli, raising the prospect of peripheral sensitization during testing [177]. Specific QST tests used in the study are discussed below.

i. Thermal Thresholds

Thermal detection thresholds have been successfully used to describe the somatosensory profile of patients with OIPN. Thermal threshold tests include warm detection threshold (WDT), cold detection threshold (CDT), heat pain threshold (HPT) and cold pain threshold. CDT assesses the function of Aδ fibers, while WDT, cold and heat pain thresholds assess the function of C-fibers [90,170]. Thermal threshold results are reported in °C and interpreted in terms of the magnitude and direction of change from baseline. Changes in thermal thresholds are described in the context of "gain of function" or "loss of function" of the affected nerve fiber. Initial injury to the nerve results in sensitization of the sensory nerve (peripheral sensitization) and gain of function. During this phase, thermal thresholds may increase (e.g. higher temperatures are reported for WDT) or decrease (e.g. lower temperatures are reported for HPT). As nerve injury progress over time, loss of function occurs, which can manifest as higher cold pain threshold, where cold pain is experienced at higher temperatures. Greater magnitudes of change from baseline indicate greater degrees of nerve dysfunction in either direction. Thermal thresholds have been shown to be reproducible tools for pain assessment [178–183].

ii. Mechanical detection threshold (MDT)

MDT is assessed using Semmes-Weinstein monofilaments (SWM) (Touch Test Sensory Kit, Neurolab.com) and assesses function of Aβ fibers. Patients with OIPN require greater gram force to elicit a response [62]. The SWM consist of 20 calibrated

monofilament fibers of equal length but varying diameters, such that they bend at a given applied force. These filament forces range from 0.008gm – 300gm. MDT is therefore scored in grams. Higher scores represent higher MDT, which reflect worsening fiber function. The SWM have been shown to be reliable and reproducible measures of mechanical force [182,184–186] and have been reliably employed for the assessment of OIPN. [44,62]

iii. Vibration perception threshold (VPT)

VPT is assessed using a quantitative graduated tuning fork (Rydel-Seiffer, US Neurologicals, Poulsbo, WA) and assesses function of Aβ fibers. When activated, the tuning fork vibrates with a frequency of 128Hz and can be felt when placed on a bony prominence. Vibration perception assessed with a tuning fork is scored on a scale of 0 – 8, with 0 representing the maximal vibration frequency and 8 representing extinction. Lower scores represent decreased vibration perception. VPT as assessed with the tuning fork has good intra- and inter-observer reliability ($\kappa = 0.90$, $p < 0.0001$ and $\kappa = 0.80$, $p < 0.0001$ respectively) and has a high correlation with sensory nerve action potential [187]. VPT decreases with age and reference data for VPT have been normalized to account for this change [170,188,189].

iv. Pin sense

The pin sense test is designed to discriminate between sharp and dull sensations and assesses Aδ fiber function, which is responsible for fast pain sensation [43]. In the presence of neuropathy, the ability to accurately discriminate between these sensations is decreased, resulting in reduced ability to correctly distinguish between sharp and dull sensation.[170,175]. Pin sense testing has been shown to be accurate and reproducible in

patients with CIPN, it is an important component of the neurological examination and is used as a component of composite tools like the TNSc©, which have been used for the assessment of OIPN [29,68,82]. Decreased ability to discriminate sharp and dull sensations is associated with worsening nerve function.

A major weakness of QST is the absence of universal standards for both testing and interpretation of results [91]. To highlight this issue, several normative data sets for thermal and pain detection threshold have been published [170,188,190–192]. In addition to the variations that exist between these datasets, the recommendation remains that the use of these normative data should only follow use of the testing protocols with which they were developed [91]. Further, interpretation of results can be done in multiple fashions, e.g. by comparison with published normative values or against an unaffected side in the same person, in the absence of normative values. Another limitation of QST is that it is a highly technical procedure and is time consuming to perform, taking approximately 1 hour.

2.2.9. Current perception threshold (CPT)

CPT takes advantage of the conduction velocity properties of nerve fibers as well as their unique depolarization and refractory periods. Specific sensory fibers types are typically depolarized at specific wavelength frequencies while other fiber types remain in their refractory periods at that frequency. CPT does not activate receptors at the ends of PAFs. So, although the nerves are stimulated, it does not elicit the corresponding sensations of pain, vibration, hot and cold, since these sensations are typically generated through activation of specific receptors on the nerves. Since PAFs contain polymodal receptors, [140,193], the ability to repeatedly stimulate a specific PAFs without receptor

activation, reduces the chances of peripheral sensitization by repeated CPT assessments. This is an advantage of CPT over QST.

During the initial stages of nerve injury, CPT values are low, meaning less current is required to activate the nerve. This is indicative of hyperesthesia, caused by peripheral sensitization from nerve damage. Over time, hypoesthesia occurs and CPT values begin to rise, due to inhibition of proper stimulus conduction by nerve damage. In the setting of CIPN, CPT values increase over the course of chemotherapy treatment [194].

The neuro-selectivity of CPT has been demonstrated in several studies. In an experiment evaluating neuro-selectivity of CPT, APs generated by sine-wave stimuli were applied to rat DRGs neurons and analyzed using intracellular recordings. The study demonstrated that Aβ neurons were selectively activated by 2000Hz stimulation at low intensity. 250Hz selectively activated Aβ and Aδ neurons. However, since noxious stimuli are preferentially conducted by Aδ fibers in the presence of tactile versus noxious stimulation, 250Hz was considered to functionally stimulate Aδ neurons. 5Hz stimulation on the other hand, activated C fiber neurons [101]. In a small study (n = 6) evaluating differential sensory block from lidocaine spinal anesthesia, recovery of Aβ fiber function as assessed by touch; Aδ fiber function as assessed by pinprick and C fiber function as assessed by cold sensation were compared to CPT assessments at 2000Hz, 250Hz and 5 Hz respectively. There was a correlation between recovery of touch and return to baseline CPT assessment at 2000Hz ($r = 0.7$, $p = 0.03$), recovery of pinprick sensation and return to baseline CPT assessment at 250Hz ($r = 0.75$, $p = 0.02$) and recovery of cold sensation and return to baseline CPT baseline assessments at 5Hz ($r = 0.67$, $p = 0.04$) [195]. [196].

CPT is assessed using the Neurometer (Neurotron, Baltimore) which has been shown to be reproducible at 2000Hz and 250Hz (ICC = 0.735 and 0.615 respectively) and moderately reproducible at 5Hz (ICC = 0.318) in healthy volunteers [197]. In another study, healthy subjects receiving femoral nerve block participated in two CPT assessments performed 24 hours apart. Within-day ICC values were between 0.66 – 0.95 and between-day ICC values were between 0.57 – 0.94, demonstrating good reliability of CPT assessments [198]. CPT assessment of the infraorbital and alveolar nerves of healthy volunteers also demonstrated good reliability properties. ICC within and between examiners ranged between 0.76 – 0.95 and 0.46 – 0.87 respectively [199]. CPT is correlated with some QST measures. For example, CPT at 2000Hz correlates with vibration thresholds and CPT at 5Hz correlates with warm detection threshold [200].

CPT has been used to evaluate sensory fiber function in carpal tunnel syndrome [110,111] and diabetic neuropathy [105–109,201]. Compared to NCS, CPT demonstrated a stronger correlation with symptoms of diabetic neuropathy and has been used to supplement physical examination in the clinical evaluation of diabetic neuropathy [108].

Age may affect CPT values. In a study of 44 healthy subjects between the ages of 32 and 87 years, CPT values were higher in older participants compared to younger ones, suggesting increased hypoesthesia among older participants [103,202]. Similarly, in elderly Japanese and Taiwanese participants, higher CPT values corresponded with increasing age [176,203]. However, other studies have reported that age has no effect on CPT [199,204]. Potential sources of this discrepancy include performance of CPT assessments at different anatomical locations e.g. fingers versus toes and population differences. Finally, clear definitions of 'healthy subjects' were not published in any of studies reviewed, and

therefore differences in criteria for 'healthy subjects' could have influenced the results. CPT values may therefore need to be standardized based on anatomic location and normalized for age if necessary.

None of the studies reviewed used CPT for the assessment of OIPN. However, two studies evaluated the use of CPT for the assessment of CIPN. In one study, sensory fiber function (CPT and QST) and QoL, were evaluated in participants (n = 26) who developed CIPN after receiving various types of chemotherapy agents for the treatment of various cancers [43]. CDT was inversely associated with CPT at 5Hz (β = -2.5, 95% CI = -4.5 – -0.5) and CPT at 2000Hz (β = -7.5, 95% CI = -11.8 – -3.3). Also, QoL, measured by the FACT/GOG-Ntx, was inversely associated with CPT at 2000Hz (β = -1.8, 95% CI = -3.5 – -0.05). These results suggest a deterioration in large, myelinated Aβ (CPT 2000Hz) and small unmyelinated C fiber (CPT 5Hz) function with the development of CIPN. The results also suggest that deterioration of large, myelinated Aβ fibers is associated with deterioration in QoL. Another study used CPT to evaluate severity of neurotoxicity in ovarian cancer patients receiving paclitaxel and carboplatin [112]. In this study, participants received chemotherapy every 3 weeks. CPT values at 2000Hz fell from baseline after the first 3 cycles of chemotherapy and rose above baseline after cycle 4. Complaints of sensory disturbances increased with each successive treatment cycle. Further, participants with a history of previous chemotherapy treatment had higher CPT values at 2000Hz and 250Hz at each assessment time point, compared to those who were chemotherapy naive. These results are consistent with deterioration in sensory fiber function that accompany chemotherapy administration. The initial decrease in CPT values represent a period of initial nerve injury, characterized by hyperesthesia or

increased sensitivity of sensory fibers. Progressive insults to the sensory fibers from subsequent chemotherapy treatments, eventually resulted in nerve damage and hypoesthesia, characterized by increased CPT values. Also, participants with a history of previous chemotherapy treatment most likely experienced damage to sensory fibers from prior treatments, which explains why they had higher CPT values compared to participants who were chemotherapy naïve. No other methods of evaluating CIPN were used in this study, so the performance of CPT against established methods of CIPN assessment could not be evaluated.

2.2.10. Assessment of OIPN-associated NP

NP requires assessment with an instrument, which evaluates elements of pain quality, pain intensity and the spatial and temporal aspects of NP [25,44,127,146,205]. Somatosensory profile of NP can be done using QST, however this is not readily available in all settings. A challenge of measuring OIPN-NP is that its symptoms often coexist with those of OIPN in the same anatomical locations. Another challenge is that some of the most commonly used tools for assessing OIPN (e.g. the NCI-CTC grading scale) are not sensitive enough to distinguish between OIPN symptoms and OIPN-NP symptoms [164]. Consequently, symptoms of OIPN-NP are often used to describe OIPN and vice versa.

Some PRQs are sensitive enough to distinguish the presence and severity of OIPN-NP [14,64,80,168]. However, OIPN-NP is often assessed only as "present" or "absent", or as part of a symptom group [48,84]. It is therefore not uncommon for OIPN to sometimes be described as "painful OIPN". It is noteworthy that most PRQs commonly used for OIPN assessments are QoL measures, used to evaluate the overall the impact of OIPN on

QoL. Thus, the use of PRQs to assess OIPN-NP does not fully capture the severity (quality, intensity, location and temporal nature) of the phenomenon.

One comprehensive instrument than can be used to assess NP in the setting of OIPN is the Neuropathic Pain Scale (NPS). The NPS is a self-report, 10-item multi-dimensional tool with a Likert response format of 0 – 10. The scale consists of 2 pain domains – pain intensity and unpleasantness. 6 items are specific to NP quality; 2 items are specific to NP location; and 1 item is related to the temporal quality of NP [206]. Higher scores represent increased NP. The NPS is valid and reliable for assessing NP [206]. NPS has good internal consistency (Cronbach's $\alpha = 0.78$, CI: 0.69 – 0.83) and test-retest reliability (ICC = 0.71) with construct validity demonstrated by significant correlation of items with the Short Form McGill Pain Questionnaire, which is a validated measure of NP [207]. Discriminant validity, predictive validity and sensitivity of the NPS have also been demonstrated in patients with NP of various etiologies [206,208]. It has also been used in assessing CIPN-associated NP [43]. Items on the NPS are scored to produce different information [209]. Each item is scored individually to obtain a profile or characterize specific NP pain dimensions. Item can also be summed to create composite scores [206,208–210]. Pain quality scores (NPS6) can be created from 6 pain quality items ("itchy", "sharp", "hot", "dull", "cold" and "sensitive") or 8 items (NPS8), which include the NPS6 and 2 spatial items ("deep pain" and "surface pain"). Also an overall pain score can be computed by summing the scores of all 10 items (NPS10) [207,209–211].

CHAPTER 3

RESEARCH DESIGN, METHODS AND DATA ANALYSIS

3.1. Design

This study is a secondary analysis of data from the Genetic Correlates of Oxaliplatin-induced Peripheral Neuropathy (GCOPN) study. A correlational descriptive design was used to guide analysis of this longitudinal study.

3.2. Primary study and sample

The GCOPN study was a prospective, descriptive, correlational study, designed to characterize the development of OIPN (S. Dorsey, PI NINR P30 NR011396-01 & N. Horiba, Pilot PI). The aims of the original study were (1) to determine the extent to which oxaliplatin-based treatment produced changes in peripheral thermal and mechanical thresholds and resultant neuropathic pain, (2) to examine systemic gene regulation associated with these changes, and (3) to examine how resulting NP affected QoL and functional status of the patients.

The study was conducted at the University of Maryland Medical Center Greenebaum Cancer Center (UMGCC), which provides primary, secondary and tertiary care for patients with a wide range of cancer diagnoses. Participants included patients diagnosed with gastrointestinal cancers who received oxaliplatin-based treatment. Inclusion criteria were (1) age between 21 to 85 years; (2) ability to speak and understand English language; (3) solid tumor diagnosis; (4) planned treatment with oxaliplatin-based therapy and (5) ability to provide informed consent. Exclusion criteria were (1) presence of pre-existing neuropathy, such as those caused by disease processes like HIV, diabetes, peripheral vascular disease, alcohol dependency and autoimmune disorders; (2) nerve

compression injuries such as spinal stenosis, brachial plexopathy and carpel tunnel syndrome; (3) previous use of neurotoxic agent in the last six months; (4) life expectancy of less than 3 months; (5) presence of major psychiatric disorders such as schizophrenia or bipolar disorder; (6) inability or unwillingness to complete study procedures, and (7) enrollment in a study which required the use of an investigational drug or biologic. A total of 19 participants were enrolled in this study. All participants (100%) were assessed at baseline before chemotherapy. Of these, 11 participants were assessed mid-study, after receiving 500mg/m^2 of oxaliplatin and 10 participants successfully completed all 3 study assessments.

3.3. Recruitment Strategy

Treating oncologists served as referral sources for participation in the study. Patients were informed about the study during their initial consultation, when treatment plans were being discussed. These patients were offered information about the study during their initial consultation visit, and staff nurses at the UMGCC identified eligible patients. Data collection and study-related procedures were performed by research staff. Initial screening through chart review was done for patients who were referred for the study. Patients who met the inclusion/exclusion criteria were recruited and enrolled into the study, after information about the study was given to the patients and informed consent obtained.

3.4. Protection of Human Subjects

The University of Maryland Institutional Review Board approved the conduct of the original study from which data was derived and used for this analysis. The study posed greater than minimal risk to the participants, due to the testing protocols as well as

the use of blood and skin samples for evaluation of genetic analysis, which was not used for the present analysis. The original data set remained secure in a password-protected external drive and all original data and forms remained securely locked in the research team office. For the present study, only de-identified data were examined and a non-human subjects research protocol was approved with the Institutional Review Board.

3.5. Method and measures used in the primary study

Demographic data including age, race, education level, cancer diagnosis, date of diagnosis, cancer surgery and date, antineoplastic regimen, anticipated number of treatment cycles as well as clinical data (e.g. height and weight) were obtained at baseline prior to receiving initial treatment. Study staff noted treatment regimen and calculated cumulative doses of oxaliplatin administered during the study. OIPN and other symptoms of toxicity were managed by the oncology team using supportive therapy and when necessary, reduction in oxaliplatin dose, and/or temporary suspension of treatment with oxaliplatin.

After written consent was obtained, study staff assessed presence of OIPN, using the NCI-CTCAE v5. Participants completed the Neuropathic Pain Scale (NPS) and FACT/GOG-Ntx (QoL) questionnaire. These measures were explained to participants and study staff was available to answer questions. Sensory fiber assessments were done using CPT testing at 2000Hz, 250Hz and 5Hz, followed by QST. The order of QST was as follows: cold detection threshold (CDT), warm detection threshold (WDT), thermal sensory limen (TSL), cold pain threshold, heat pain threshold (HPT), mechanical detection threshold (MDT), pin sense, and vibration detection threshold (VDT). Standardized sets of instructions were given to participants during QST testing. Other

assessments of motor function performed in the primary study that are not addressed in the present analysis include grip strength and DTR.

The same sets of assessments and questionnaires were administered after participants received 500mg/m^2 of oxaliplatin and after they completed all chemotherapy. Participants with NCI-CTC grade $\geq$ 1 were considered to have OIPN because NCI-CTC grade 1 defines mild CIPN symptoms that do not interfere with activities of daily living.

3.5.1. Current Perception Threshold

CPT assessment was done using the Neurometer® (Neurotron, Baltimore) and the influence of OIPN on nerve fiber response to CPT testing is summarized in Table 4. Prior to testing, temperature of the participant's palm was obtained and recorded using a thermometer. The middle finger of the non-dominant hand was cleansed to remove dead skin and oil residue. Two 12 mm diameter gold electrodes containing conductive gel were attached to the finger. Alternating current in the range of 0.01 to 9.99 milliamperes (mA) was delivered in sinusoid waveform at a frequency of 2000Hz. After determining the sensory threshold, an automated electrical current stimulus was applied to the finger above and below the predetermined sensory threshold. Participants provided responses regarding the presence or absence of electrical stimuli, via a feedback button. To eliminate bias, both the tester and participant were blinded to timing of electrical stimulus. The procedure was repeated for up to 20 cycles until CPT value was determined. The same procedure was performed with frequencies of 250Hz and 5Hz. If a CPT value could not be determined at a frequency, the procedure was repeated at that frequency for a total of three times and aborted after the third attempt.

Table 4: Current perception threshold, fiber assessed and their responses to OIPN

Current Perception Threshold Test (Frequency in Hz)	PAF Assessed	Influence of CIPN (Current required to stimulate PAF in mA)
CPT 2000Hz	Aβ	Early: Decreased current Late: Increased current
CPT 250Hz	Aδ	Early: Decreased current Late: Increased current
CPT 5Hz	C	Early: Decreased current Late: Increased current

3.5.2. Quantitative Sensory Testing

QST was performed using protocols previously established in the literature [170,175,190,194]. QST test performed and the sequence of quantitative sensory testing has been described above.

i. Thermal detection threshold

Thermal detection thresholds were obtained using the Pathway Model ATS (Medoc, Israel) Peltier device. A 16 x 16 mm surface area thermode with a baseline temperature of 32°C was placed on the surface of the middle finger on the non-dominant hand. The temperature of the thermode was decreased or increased at a rate of 1°C/s in an automated fashion. Upon detection of cold or warmth participants pressed a button, which recorded the temperature at which the sensation was detected. This was repeated three times with a 6-second pause between testing, and the mean temperature recorded as the CDT or WDT respectively. For pain thresholds, temperature of the thermode was increased (for HPT) or decreased (for cold pain threshold) at the rate of 1°C/s and participants were asked to press the feedback button when they could no longer tolerate

the heat or cold sensations. These temperatures were recorded as HPT and cold pain threshold respectively. To assess TSL, paradoxical cold and warm sensations were applied via the thermode and participants were asked to use the feedback button to indicate when they felt a change in temperature and whether the sensation was warm or cold. To ensure participant safety and reduce the risk of injury, automatic temperature cutoffs of 0°C and 51°C were programmed into the Pathway device.

ii. MDT

MDT was assessed using Semmes-Weinstein monofilaments (SWM) (Touch Test Sensory Kit, my Neurolab.com). Participants closed their eyes and Semmes-Weinstein monofilaments (SWM) were applied to the surface of the middle finger of the non-dominant hand in a perpendicular fashion, until the monofilament began to bend. This was held for 1 second and then promptly removed. Starting with the smallest diameter monofilament, testing was repeated three times. Monofilament size was progressively increased until participant could feel at least one of the attempts. That monofilament size was recorded, as the MDT.

iii. VPT

A calibrated tuning fork was used to assess vibration threshold. After initiating vibration on the fork, the vibrating fork was placed on the bony prominence of the middle finger of the non-dominant hand and participants were asked to tell the tester when vibration sensation ceased. The reading on the tuning fork was noted. This was repeated three times.

iv. Pin sense

Pin-sense testing was performed using a pin and a paper clip. With their eyes closed, participants were introduced to the sharp sensation and dull sensation. After 30 seconds, three sharp and three dull sensations were applied in random order and participants were asked to identify the sensation after each stimulus was applied. Responses were recorded.

3.6. Data Analysis

3.6.1. Descriptive analysis

Exploratory data analysis was performed to describe the sample. Categorical variables such as gender, education and treatment regimen were reported as frequencies and percentages. Means and standard deviations with ranges were used to describe continuous variables such as age, BMI, and body surface area (BSA). Participants were stratified into groups based on the

presence or absence of OIPN – those who developed OIPN (NCI-CTC $\geq$ 1) and those who did not develop OIPN (NCI-CTC = 0). Composite scores were computed for the NPS and FACT/GOG-Ntx. QST data was examined to determine sensory fiber gain and/or loss of function associated with OIPN and OIPN-NP. Variables that were used for descriptive analysis are presented in Table A6 and A7.

3.6.2. Hypotheses testing

Linear mixed modeling (LMM) were used to test the hypotheses of the study. This technique was developed to analyze data with repeated measures and non-independent residuals by including random effects in the model [212]. In LMM, the level of measurement of the outcome variable is continuous and normally distributed. LMM uses all available data when missing data or dropouts occur for longitudinal observations. In

techniques like ANOVA, complete datasets for all participants are required and participants are eliminated from analysis due to list wise/case wise deletion of cases with any missing data point, resulting in biased estimation and loss of power. Thus, LMM is well suited for analysis of longitudinal studies, where non-independence and missing data are common.

To examine the associations between predictors and continuous outcome variables like QoL, LMM was used. A random intercept of the participants was included in each statistical model. The intraclass correlation (ICC) of the corresponding null model was calculated to ensure that the use of LMM is appropriate. In all models, parameter estimates along with the 95% confidence intervals were computed for each predictor. A p-value < 0.05 was considered significant.

Sample size being pre-determined, post-hoc power analysis was performed using procedures outlined by Gelman (2007) [213]. The analysis assumed the study sample to be an accurate representation of the population and that the model-detected effects accurately characterized the association between variables in the population. After accounting for missing data and repeated measurements, the specific observed power of each model to detect a significant effect was calculated by determining the proportion of samples in which the model detected a significant association between the variables represented in the model, out of 10,000 samples obtained from a simulated population. A proportion of 0.8 was considered sufficient power. To determine the sample size required to achieve a power of 0.8, assuming the model-based effect was indeed true and a large effect size, a series of simulations were conducted with increasing sample sizes. The power detected as a function of sample size was then plotted to determine sample size.

All data analysis was performed using SPSS (IBM, New York) version 23 package, except post-hoc power analysis which was performed using R, a publically available statistical computing program (https://www.r-project.org).

3.6.3. Analysis plans for study aims

Aim 1a: Describe the associations between CPT (5Hz, 250Hz, and 2000 Hz) and QST (vibration perception, pin sense, warm detection, cold detection and mechanical detection thresholds).

Hypothesis: CPT 5Hz will be negatively associated with pin sense and positively associated with warm detection threshold; CPT 250Hz will be negatively associated with pin sense and cold detection threshold; and CPT 2000Hz will be negatively associated with VPT and positively associated with MDT.

To test each of the hypotheses, separate LMM regression models were used to examine the associations. For example, CPT 2000Hz was the outcome variable in the corresponding LMM. Fixed effects were VPT or MDT. Random effects were the participants, which accounts for correlation within each subject. A similar approach was used to examine the other hypotheses regarding CPT 250Hz and CPT 5Hz. Besides the aforementioned hypotheses, the potential relationships between each of the CPT measures and QST measures were examined using similar LMM methods.

Aim 1b: Determine if CPT (5Hz, 250Hz, 2000Hz) vary by d-OIPN (NCI-CTC) status.

Hypothesis: CPT at 5Hz, 250Hz and 2000Hz will be higher in patients with d-OIPN compared to those without OIPN.

To test the hypothesis, three separate models were used to examine the association. Each of the CPT measures was the outcome variable in the models. Predictor

variable was d-OIPN status. To account for ICC within each subject, participants were treated as random effects.

Aim 2a: Describe the progression of OIPN-NP (NPS score, cold pain and heat pain thresholds) over the course of oxaliplatin treatment.

For each time point, sum scores of items on the NPS10 (see section 2.5) was computed to determine overall OIPN-NP score [210]. A spaghetti plot was created to illustrate the progression of OIPN-NP over time in participants.

Aim 2b: Explore the association between OIPN-NP (NPS, cold pain and heat pain thresholds) and d-OIPN (NCI-CTC).

Hypothesis: NPS scores will be positively associated with d-OIPN while cold pain and heat pain thresholds will be negatively associated with chronic OIPN

To examine this relationship, regression models were created using LMM, to evaluate the bivariate association between OIPN-NP and d-OIPN. OIPN-NP was the outcome variable and d-OIPN will be the predictor. Since NPS scores, cold pain and heat pain threshold are used to assess OIPN-NP, separate models were created to examine the relationship between d-OIPN and each of these measures. Participants were added to the models as a random effect to account for ICC within participants.

Aim 2c: Determine if OIPN-NP (NPS, cold pain and heat pain thresholds) and d-OIPN (NCI-CTC) have independent associations with QoL (FACT/GOG-Ntx).

Hypothesis: NPS score, cold pain and heat pain thresholds will be negatively associated with QoL (FACT/GOG-Ntx). Also, d-OIPN (NCI-CTC) will be negatively associated with QoL.

LMM was used to compute a regression model, examining the association

between QoL (FACT-G scores), OIPN-NP and d-OIPN. Because the Ntx subscale was added to the FACT-G later in the study, the FACT-G scores only were used to assess QoL. The outcome variable in the models was QoL, while OIPN and OIPN-NP (NPS10 scores) were the predictors in the model. Random effects were included to account for ICC within subject. Since it is established that QoL is reduced in the presence of OIPN [15,65], estimates of the variance in QoL among participants that is explained by the presence of OIPN was first be determined. Consequently, NPS scores was then introduced into the model to provide an estimate of the impact of OIP-NP on QoL.

In all models, parameter estimates along with the 95% confidence intervals were computed for each predictor. Also, when introduced into any of the LMMs, the variable "Time" represented assessment time points (i.e. at baseline before receiving oxaliplatin, after receipt of 500mg/m^2 of oxaliplatin after the end of treatment).

CHAPTER 4

RESULTS

4.1. Sample Characteristics

A total of 19 participants were enrolled in the study. Of those enrolled, 10 (52.4%) participants were available for assessment at the mid-point of the study (i.e. after receiving 500mg/m2 of oxaliplatin) and 9 (47.6%) participants completed assessments at all three time points. Sample characteristics are shown in Table 5. The most common cancer diagnoses were colon cancer (42.1%) and pancreatic cancer (26.3%). The majority of the participants were Caucasian males, and included 7 (36.8%) women and 8 (42.4%) participants who were either African American or Asian. The mean age of the participants was 55.2 years. Many of the participants (47.7%) had associates degrees, most were diagnosed with stage IV cancer (63.3%) and had undergone surgery for removal of the tumor prior to initiation of chemotherapy (57.9%).

4.2. Research Aim 1a

Describe the associations between CPT (5Hz, 250Hz, and 2000 Hz) and QST (vibration perception, pin sense, warm detection, cold detection and mechanical detection thresholds).

4.2.1. Descriptive and exploratory data analysis

The data were first restructured, such that each case represented an observation and not the individual. Table 6 shows the average values of CPT and QST at three time points. Boxplots of CPT and QST variables over time are shown in Appendices A1 – A8. The intra-class coefficients (ICC) were computed and indicated that random effects models were needed for fitting the data. The normality assumption was not violated for

the CPT measures (all skewness <1). Figures 2 to 4 show the spaghetti plots for CPT 2000, CPT250 and CPT5 over time. There was variation in baseline values (intercept) and in the change over time (slope) for all the outcome variables, suggesting that a random intercept model (RI) and/or random slope model (RS) are needed.

4.2.2. Bivariate Associations between CPT and QST

LMM was used to examine bivariate associations between QST measures (MDT, VPT, Pin Sense, CDT, WDT and CDT) and CPT. Table 7 summarizes the model fit indices of the three models for each of the QST measures on CPT. Random intercept model with time (RI + Time) was the most parsimonious model for CPT 2000Hz while RI only model was the most parsimonious model for CPT 250Hz and CPT 5Hz. Table 8 summarizes the relationships between CPT and each QST measure respectively. CPT 2000Hz was associated with MDT ($\beta = 269.59$, $p = 0.008$), VPT ($\beta = -44.55$, $p=0.045$), and WDT ($\beta = 9.00$, $p = 0.030$). CPT 250Hz was associated with WDT ($\beta= 4.24$, $p = 0.027$); no association between CPT 5Hz and any of the quantitative sensory tests was found.

4.3. Research Aim 1b

Determine if CPT (5Hz, 250Hz, 2000 Hz) varies by d-OIPN (NCI-CTC) status.

4.3.1. Descriptive and exploratory data analysis

At baseline, one participant reported the presence of peripheral neuropathy, which was unrelated to the administration of oxaliplatin, and the participant was subsequently excluded leaving 18 participants available for analysis. At mid-point (after receiving 500mg/m^2 of oxaliplatin), 3 (15.8%) participants developed Grade 2 OIPN. At the end of oxaliplatin treatment, a total of 6 (31.6%) participants had developed OIPN, 2 (10.5%) of

Table 5: Sample Characteristics at Baseline (n=19)

Sample Characteristics	N (%)	Mean (SD)	Range
Age (years)		55.2 (12.8)	34 - 76
Gender			
Male	12 (63.2%)		
Female	7 (36.8%)		
Race			
Asian	1 (5.3%)		
Black/African American	7 (36.8%)		
White/Caucasian	11 (57.9%)		
Level of Education			
High School	5 (26.3%)		
Associates/Diploma	9 (47.7%)		
Baccalaureate	1 (5.3%)		
Graduate Degree	2 (10.5%)		
Missing	2 (10.5%)		
Weight (kg)		74.5 (17.6)	51.2 – 124.1
Height (cm)		169.7 (9.8)	147 – 185
BMI		25.9 (5.4)	19.3 – 39.2
Body Surface Area (m2)		1.9 (0.2)	1.54 – 2.39
Cancer Diagnosis			
Colon Cancer	8 (42.1%)		
Rectal Cancer	4 (21.1%)		
Pancreatic Cancer	5 (26.3%)		
Other	2 (10.5%)		
Cancer Stage			
Stage 1	1 (5.3%)		
Stage 3	6 (31.6%)		
Stage 4	12 (63.2%)		
Chemotherapy Regimen			
mFOLFOX-6	4 (21.1%)		
FOLFOX-6	4 (21.1%)		
FOLFIRINOX	5 (26.3%)		
XELOX	2 (10.5%)		
Other	1 (5.3%)		
Missing	3 (15.8%)		
Past Cancer Treatment			
None	6 (31.6%)		
Surgery	11 (57.9%)		
Radiation Therapy	1 (5.3%)		
Surgery and Radiation Therapy	1 (5.3%)		
Concurrent Treatment			
None	13 (68.4%)		
Surgery	3 (15.8%)		
Radiation Therapy	1 (5.3%)		
Missing	2 (10.5%)		

Table 6: Observation level descriptive statistics for outcome measures

Variable	Number of observations	Mean ± SD	Skewness	ICC
CPT 2000Hz	32	331.88 ± 97.43	0.633	0.27
CPT 250Hz	34	103.50 ± 44.90	0.165	0.52
CPT 5 Hz	36	51.36 ± 33.16	0.565	0.67
FACT-G	37	50.18 ± 10.26	-0.114	0.63
Cold Pain Threshold (°C)	34	2.21 ± 3.22	1.575	0.43
Heat Pain Threshold (°C)	34	47.49 ± 3.92	-0.807	0.48
NPS-10 Score	23	11.43 ± 14.75	1.542	0.12

Note: ICC = Intra-class correlation coefficient.

Table 7: Model fit indices for bivariate relationship between CPT and QST

CPT	Model	Model Parameter	Parameter Estimates (df)				
			MDT	VPT	Pin Sense	CDT	WDT
2000Hz	RI	AIC	382.014 (4)	381.25 (4)	388.992 (4)	364.693 (4)	358.644 (4)
		BIC	387.877	387.11	394.854	370.298	364.249
	RI + RS	AIC					
		BIC	##	##	##	###	##
	RI + Time	AIC	380.219 (5)	378.914 (5)	385.740 (5)	362.389 (5)	357.133 (5)
		BIC	387.548	391.242	398.069	369.395	364.139
250Hz	RI	AIC	345.527 (4)	344.132 (4)	346.079 (4)	324.194 (4)	319.440 (4)
		BIC	351.513	350.118	352.065	329.930	325.176
	RI + RS	AIC					
		BIC	###	###	###	###	###
	RI + Time	AIC	346.695 (5)	345.396 (5)	347.570 (5)	325.682 (5)	320.867 (5)
		BIC	354.177	352.879	355.052	332.852	328.037
5Hz	RI	AIC	352.689 (4)	352.847 (4)	353.696 (4)	333.839 (4)	332.743 (4)
		BIC	359.023	359.181	360.030	339.944	338.849
	RI + RS	AIC				335.822 (5)	
		BIC	###	###	###	343.454	###
	RI + Time	AIC	354.618 (5)	354.419 (5)	355.580 (5)	335.716 (5)	334.742 (5)
		BIC	362.536	362.336	363.498	343.348	342.374

Note: RI = Random intercept, RS = Random slope, df = Degree of freedom, ## = Inestimable model – Validity of results cannot be ascertained, ### = Inestimable model – Validity of model fit is uncertain, CPT = Current perception threshold, MDT = Mechanical detection threshold, VPT = Vibration perception threshold, CDT = Cold detection threshold, WDT = Warm detection threshold

Table 8: Linear Mixed models for associations between CPT and QST

CPT (Hz)	Parameter Estimates for Quantitative Sensory Tests				
	MDT	VPT	Pin Sense	CDT	WDT
2000 RI+Time	**β = 269.59 CI = 76.85 – 462.34 p = 0.008**	**β = -44.55 CI = -87.95 – -1.15 p = 0.045**	β = 10.73 CI = -32.05 – 53.51 p = 0.610	β = -2.67 CI = -9.83 – 4.48 p = 0.446	**β = 9.00 CI = 0.93 – 17.07 p = 0.030**
250 RI Only	β = 41.99 CI = -28.20 – 112.19 p = 0.231	β = -17.66 CI = -36.76 – 1.43 p = 0.068	β = -7.07 CI = -23.06 – 8.9 p = 0.368	β = -0.95 CI = -4.38 – 2.48 p = 0.573	**β = 4.24 CI = 0.53 – 7.94 p = 0.027**
5 RI Only	β = 15.36 CI = -14.94 – 45.65 p = 0.309	β = 6.32 CI = -7.28 – 19.92 p = 0.350	β = -1.58 CI = -12.69 – 9.52 p = 0.771	β = -0.82 CI = -3.22 – 1.58 p = 0.487	β = 1.83 CI = -0.95 – 4.6 p = 0.186

Note: **Bold** = Statistically significant, CI = confidence intervals, CPT = Current perception threshold, MDT = Mechanical detection threshold, VPT = Vibration perception threshold, CDT = Cold detection threshold, WDT = Warm detection threshold; Outcomes: CPT measure; Each of the QST measures (predictors) was fit with one CPT measure individually in separate models. CPT 2000Hz models included time as a covariate.

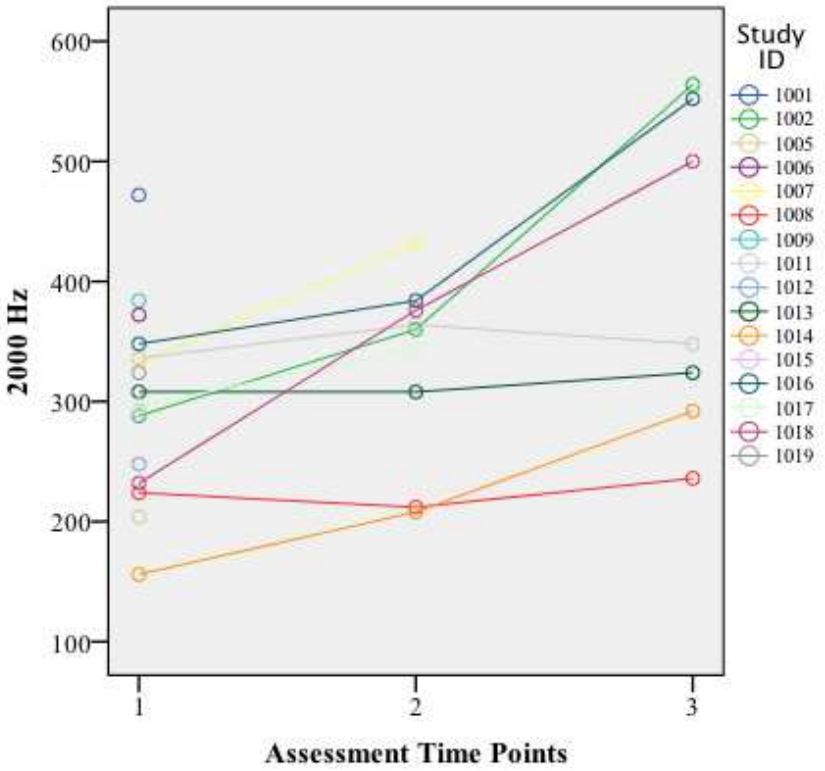


Figure 2: Spaghetti plot for CPT 2000Hz

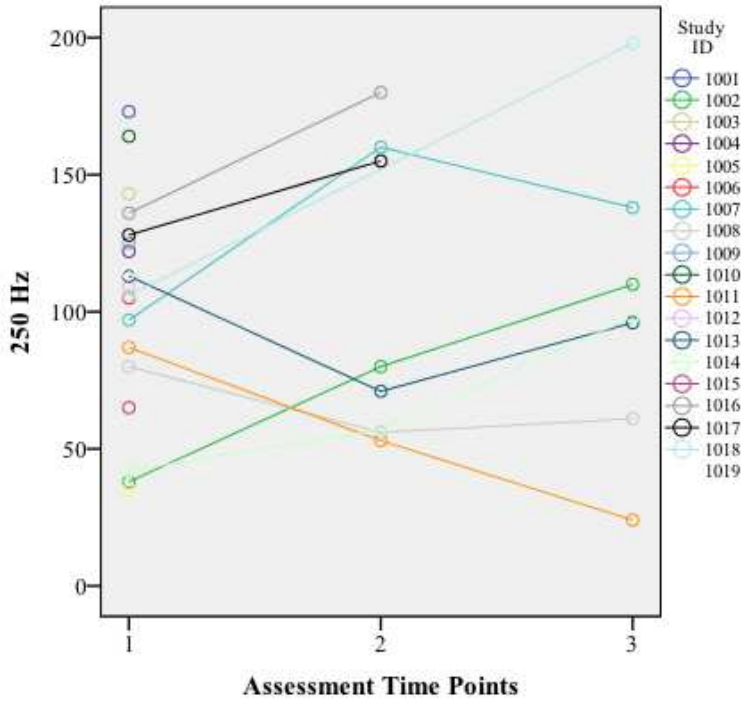


Figure 3: Spaghetti plot for CPT 250Hz

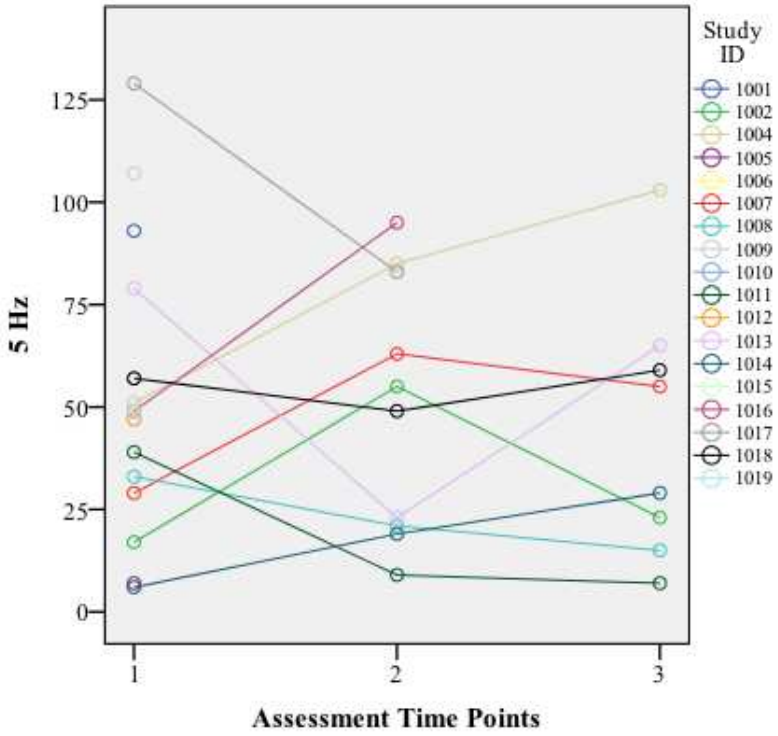


Figure 4: Spaghetti plot for CPT 5Hz

Table 9: Prevalence of OIPN at Assessment Time Points (n=18)

Time point	N (%)
Treatment midpoint (500mg/m^2)	
No OIPN	7 (37%)
Grade 2 OIPN	3 (16%)
Missing	9 (47%)
End of Treatment	
No OIPN	3 (16%)
Grade 1 OIPN	2 (11%)
Grade 2 OIPN	4 (21%)
Missing	10 (53%)

Note: OIPN Status was determined using the Peripheral Sensory Neuropathy assessment on the NCI-CTC grading scale v. 5

whom had Grade 1 OIPN and 4 (21.1%) of whom had Grade 2 OIPN. Among the three participants who developed OIPN at the mid-point assessment, two continued to have OIPN at the end of treatment in addition to 4 new cases of OIPN. Table 9 illustrates the prevalence of OIPN among the participants at midpoint and end of study.

4.3.2. Bivariate associations between d-OIPN and current perception threshold (CPT)

D-OIPN was re-coded into a dummy binary variable. CPT (CPT 2000Hz, CPT 250Hz and CPT 5Hz) was the outcome variable in the models. Since participants developed d-OIPN at different time points (midpoint vs. post treatment), d-OIPN was treated as a time-varying predictor in the model. At each stage, model fit was assessed using AIC and BIC. Model fit indices are summarized in Table 10. The RI + Time model was the most parsimonious model for CPT 2000Hz and CPT 250Hz, while RI only model was the most parsimonious model for CPT 5Hz. The final models examining the bivariate association between d-OIPN and CPT are summarized in Table 11. There was no significant association between CPT and d-OIPN. The calculated observed power for the

associations between OIPN and CPT at 2000Hz, 250Hz and 5Hz were 0.22, 0.21 and 0.07 respectively.

Table 10: Model fit indices for Bivariate association between OIPN (predictor) and CPT (outcome)

Model	Model Parameters	Parameter estimates (df)		
		CPT 2000Hz	CPT 250Hz	CPT 5Hz
Random Intercept	AIC	381.094 (4)	353.846 (4)	353.785 (4)
	BIC	386.957	359.951	360.119
Random Intercept + Random Slope	AIC	382.914 (5)	355.823 (5)	###
	BIC	390.242	363.455	
Random Intercept + Time	AIC	377.884 (5)	345.271 (5)	355.578 (5)
	BIC	385.213	352.754	363.496

Note: ## = Inestimable model – validity of results could not be ascertained

Table 11: Final model for bivariate association between OIPN (predictor) and CPT (outcome) using most parsimonious models

OIPN Status	Parameter estimates for CPT		
	CPT 2000Hz	CPT 250Hz	CPT 5Hz
OIPN present	β = 60.51 CI = -12.96 – 133.98 p = 0.102	β = 20.01 CI = -17.15 – 57.18 p = 0.276	β = 0.65 CI = -18.9 – 20.29 p = 0.946

Note: CI = confidence intervals, OIPN = oxaliplatin-induced peripheral neuropathy

4.4. Research Aim 2a

Describe the progression of OIPN-NP (NPS score, cold pain and heat pain thresholds) over the course of oxaliplatin treatment.

4.4.1. Descriptive and exploratory data analysis

Table 12 shows the descriptive analysis of OIPN-NP measures (cold pain threshold, heat pain threshold and NPS scores) at all three time points. Cold and heat pain thresholds were available for 16 (89%) participants at baseline, 9 (50%) participants at

midpoint and 8 (44%) participants at the end of treatment. Of these 7 (39%) participants had cold pain and heat pain threshold assessment for all assessment time points. Participants experienced increases in cold pain threshold (or decreased cold pain tolerance evidenced by increased threshold temperatures) and decreases in heat pain threshold (or decreased heat pain tolerance evidenced by decreased threshold temperatures) during treatment. Mean cold pain threshold temperatures at baseline, midpoint and end of treatment were 1.40°C (median = 0°C), 3.4°C (median = 0.47°C) and 2.9°C (median = 2.23°C) respectively, representing an increase in cold pain threshold from baseline at both midpoint and end of treatment. Mean heat pain threshold temperatures at baseline, midpoint and end of treatment were 47.8°C (median = 49.8°C), 46.5°C (median = 46.4°C) and 47.5°C (median = 48.9°C) respectively, demonstrating a decrease in heat pain threshold from baseline at both midpoint and end of treatment. Spaghetti plots showing baseline variation and changes over time in NPS scores, cold pain threshold and heat pain thresholds are illustrated in figures B1 to B3.

Of the 18 participants included in the analysis, NPS scores were available for 8 (42.1%) participants at baseline, for 7 (36.8%) participants at the midpoint (after receiving 500mg/2 of oxaliplatin) and 8 (42.1%) participants at the end of treatment. A total of 6 participants (33%) had NPS scores at all 3 assessment time points. At baseline 2 out of 8 participants (25%) reported NP not associate with oxaliplatin administration. At midpoint, all 7 participants (100%) reported OIPN-NP and at the end of treatment, 5 out of 8 participants (63%) reported OIPN-NP. At baseline, midpoint and end of treatment mean NPS scores were 5.8 (median = 0), 16.4 (median = 10) and 12.8 (median = 10.5) respectively. In summary, most of the study participants experienced new onset or

worsening OIPN-NP during oxaliplatin treatment which persisted through the end of oxaliplatin treatment.

Table 12: Descriptive analysis of neuropathic pain measures

	N	Minimum	Maximum	Mean (SD)	Median	Skewness (SE)	Kurtosis (SE)
Cold pain threshold (°C)							
Baseline	16	-0.13	5.6	1.4 (2.1)	0	1.1 (0.6)	-0.3 (1.1)
500mg/m^2	9	-0.03	11.9	3.4 (4.8)	0.47	1.3 (0.7)	-.04 (1.4)
End of Tx.	8	0	7.6	2.9 (2.9)	2.27	0.6 (0.7)	-1.2 (1.5)
Heat pain threshold (°C)							
Baseline	16	37.5	51.1	47.8 (3.9)	49.78	-1.6 (0.6)	2.1 (1.1)
500mg/m^2	9	41.1	51.1	46.5 (4.2)	46.37	-.08 (0.7)	-2.0 (1.4)
End of Tx.	8	42.9	51.1	47.5 (4.0)	48.85	-0.3 (0.8)	-2.4 (1.5)
Neuropathic Pain Scale							
Baseline	8	0	31	5.8 (11.5)	0	1.9 (0.8)	3.4 (1.5)
500mg/m^2	7	3	54	16.4 (17.9)	10	1.9 (0.8)	3.9 (1.6)
End of Tx.	8	0	41	12.8 (16.6)	10.5	1.0 (0.8)	0.6 (1.5)

Note: Neuropathic pain scale range = 0 – 100, with higher scores representing higher pain intensity. Tx. = Treatment

4.5. Research Aim 2b

Explore the association between OIPN-NP (NPS, cold pain, and heat pain thresholds) and d-OIPN (NCI-CTC).

4.5.1. Descriptive and exploratory data analysis

Table 6 shows mean scores for all three NP measures (NPS10, cold pain and heat pain threshold), while Tables A1 – A3 show the median values for OIPN-NP measures, across the three time points by OIPN status. ICC computed for OIPN-NP measures were 0.12, 0.43 and 0.48 for NPS score, cold pain threshold and heat pain threshold, respectively, indicating that random effects models were needed to fit the data. (See Table 6). Spaghetti plots for OIPN-NP measures (NPS scores, cold pain and heat pain thresholds) showed variations in baseline values and in change over time for all pain measures (Figure B1 – B3), thus justifying random intercept and/or random slope models to fit the data. NPS scores and cold pain threshold had skewness of 1.542 and 1.575

respectively and were each transformed to achieve a normal distribution. After transformation, skewness for NPS scores and cold pain threshold were 0.123 and 0.493 respectively. Skewness for heat pain threshold was -0.807.

4.5.2. Bivariate association between measures of OIPN-NP and d-OIPN

Measures of OIPN-NP (NPS, cold pain threshold and heat pain threshold) were outcome variables. Since participants developed d-OIPN at different time points, d-OIPN was treated as a time-varying covariate in the model. The data were restructured as previously described in section 4.2.1. LMM was used to examine bivariate associations between OIPN and OIPN-NP measures. Table 13 summarizes the model fit indices of d-OIPN on the three models for each of the NP measures. Random intercept model with time (RI + Time) was the most parsimonious model for NPS scores, while random intercept only (RI) model was the most parsimonious model for cold pain and heat pain thresholds. Table 14 summarizes the relationship between d-OIPN and OIPN-NP measures. None of the associations between d-OIPN, NPS scores, cold pain threshold or heat pain threshold reached significance. The calculated observed power for the bivariate association between d-OIPN and NPS scores, cold pain threshold and heat pain threshold were 0.72, 0.36 and 0.38 respectively.

Table 13: Model fit indices for bivariate associations between OIPN (predictor) and measures of OIPN-NP (outcome)

Model	Model Parameters	Parameter estimates (df)		
		Neuropathic Pain Scale	Cold Pain Threshold	Heat Pain Threshold
Random Intercept	AIC BIC	##	166.959 (4) 172.945	193.625 (4) 199.733
Random Intercept + Random Slope	AIC BIC	##	##	##
Random Intercept + Time	AIC BIC	174.891 180.346 (5)	164.846 (5) 172.329	195.010 (5) 202.642

Note: ## = Inestimable model – validity of results could not be ascertained

Table 14: Final model for bivariate association between OIPN (predictor) and measures of OIPN-NP (outcome) using most parsimonious models

OIPN Status	Parameter estimates for NP measures		
	NPS Scores	Cold Pain Threshold	Heat Pain Threshold
OIPN Present	β = -9.26 CI = -21.77 – 3.24 p = 0.138	β = 1.09 CI = -0.87 – 3.05 p = 0.257	β = 0.21 CI = -2.59 – 3.00 p = 0.880

4.6. Research Aim 2c

Determine if OIPN-NP (NPS, cold pain and heat pain thresholds) and d-OIPN (NCI-CTC) have independent associations with QoL (FACT-G).

4.6.1. Descriptive and exploratory data analysis

Table 6 shows mean FACT-G scores while Table A4 shows the median FACT-G scores across the three time points by OIPN status. Box plot for FACT-G scores is shown in Figure 5. ICC of 0.63 was computed for FACT-G scores suggesting that random

effects models were needed to fit the data. Spaghetti plot for FACT-G scores (Figure 6) showed variation in baseline values and in change over time, suggesting a random intercept (RI) model and/or random slope (RS) model would be appropriate for analyzing this data. The normality assumption was not violated (skewness = -0.114), therefore the data was assumed to be normally distributed. Median FACT-G scores by OIPN-NP presence as assessed using the NPS is shown in figure 7. All predictors in this model (OIPN-NP measures and OIPN) were treated as time-varying in the models.

4.6.2. Bivariate analysis to assess association between d-OIPN and QoL

To determine if OIPN-NP (NPS, cold pain threshold and heat pain threshold) and d-OIPN have independent associations with QoL (FACT-G), LMM was used to examine bivariate associations between presence of d-OIPN and QoL. The measures of OIPN-NP were examined as fixed effects. Table 15 summarizes the model fit indices for FACT-G scores. RI + Time was found to be the most parsimonious model to estimate the association between d-OIPN and FACT-G scores. As shown in Table 16 model 1, the association between d-OIPN and FACT-G scores was not significant. The calculated observed power for this bivariate association was 0.07.

4.6.3. Analysis to assess independent association of d-OIPN and OIPN-NP with QoL

Table 16 models 2, 3 and 4 summarize the fixed effects of OIPN-NP measures on FACT-G scores. NPS scores have a significant association with FACT-G scores ($\beta = 0.34$, $p = 0.002$), with OIPN in the model. To estimate the final model (Model 5), non-significant fixed effects were excluded and this improved the model fit. NPS score was found to have a significant association with FACT-G scores ($\beta = 0.273$, $p = 0.016$). In this sample,

higher NPS scores was associated with higher QoL (higher FACT-G scores). This finding is opposite to what is reported in the literature.

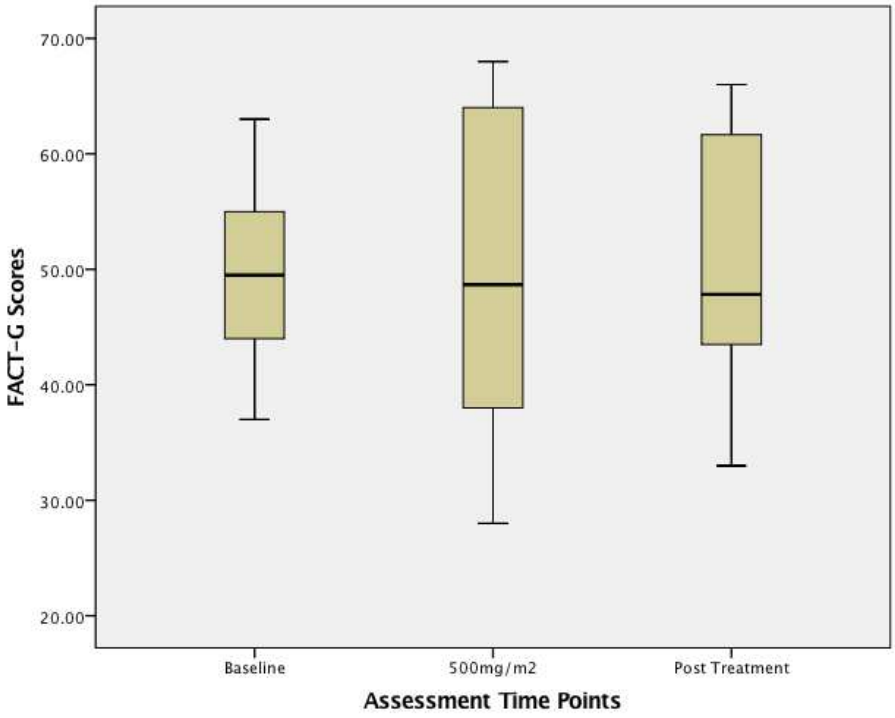


Figure 5: FACT-G scores across assessment time points

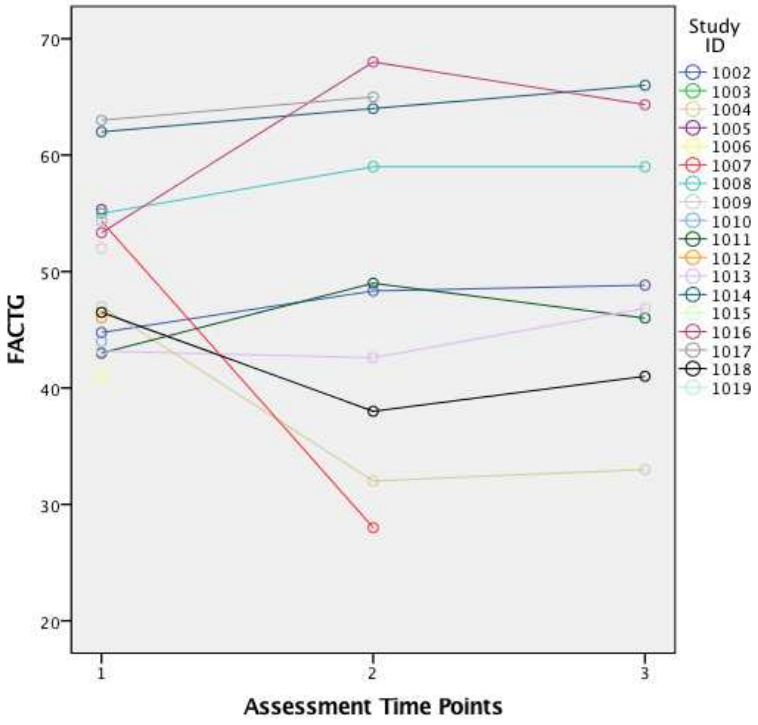


Figure 6: Scatterplot for FACT-G across assessment time points

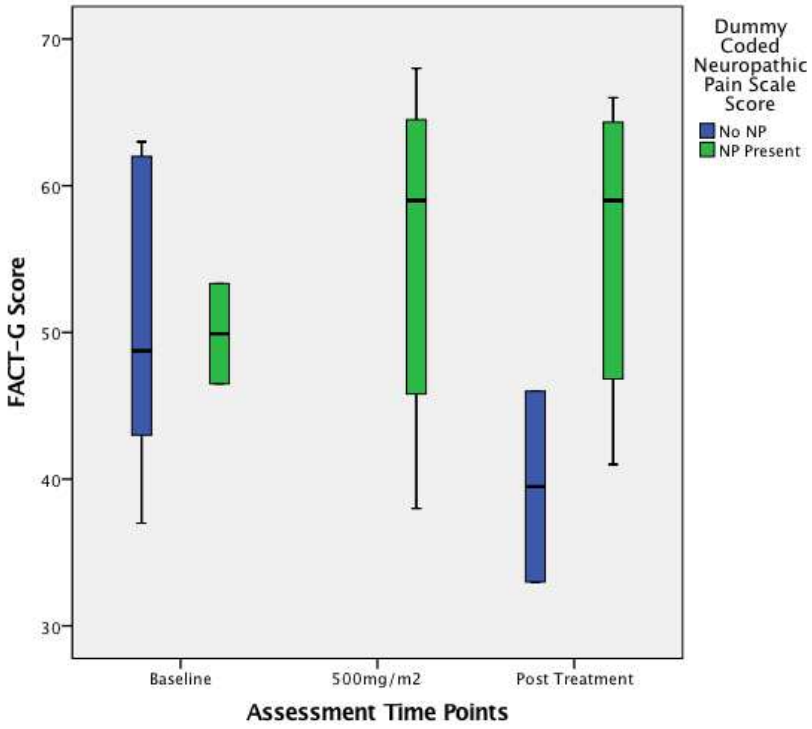


Figure 7: FACT-G scores by NP presence

Table 15: Model fit indices for bivariate associations between OIPN (predictor) and quality of life (FACT-G) (outcome)

Model	Model Parameters	Parameter estimate (df)
Random Intercept	AIC	272.267 (4)
	BIC	278.711
Random Intercept + Random Slope	AIC	##
	BIC	
Random Intercept + Time	AIC	267.334 (5)
	BIC	275.252

= inestimable model – validity of results could not be ascertained.

Table 16: Comparison of Linear mixed models with NP measures as fixed effects estimating FACT-G scores

Model	β (SE)	t-statistic	p-value	Model fit Statistic		
				AIC	BIC	df
Model 1				267.334	275.252	5
OIPN	1.56 (3.61)	0.433	0.669			
Time	-0.06 (0.11)	0.506	0.617			
Model 2				150.533	157.080	6
OIPN	0.35 (2.23)	0.156	0.879			
Time	-0.04 (0.07)	0.604	0.556			
NPS Score	**0.34 (0.09)**	**3.676**	**0.002**			
Model 3				246.555	255.534	6
OIPN	5.74 (4.16)	1.374	0.181			
Time	-0.23 (0.15)	1.517	0.140			
Cold Pain	0.86 (0.47)	1.834	0.077			
Model 4				249.463	258.442	6
OIPN	4.01 (4.28)	0.938	0.357			
Time	-0.13 (0.15)	0.844	0.406			
Heat Pain	0.22 (0.41)	0.543	0.591			
Model 5				146.682	151.904	5
NPS Score	**0.273 (0.09)**	**2.741**	**0.016**			
Time	0.589 (1.11)	0.529	0.607			

Note: **Bold** = statistically significant

4.7. Summary of results

The aims of this secondary data analysis were to ascertain construct validity of CPT, by determining the bivariate associations between CPT and QST measures of sensory nerve function in the setting of OIPN. Further, this analysis sought to examine the association between OIPN and OIPN-NP, and to determine if OIPN and OIPN-NP have independent associations with QoL. The major findings of this study are summarized below:

1. CPT 2000Hz which assesses Aβ was associated with vibration perception and WDT, which are measures of Aβ and C fiber function respectively. Both associations are statistically significant. CPT 250Hz which assess Aδ fiber is associated with WDT. There was no significant association between CPT 5Hz and any of the quantitative sensory tests of sensory nerve fibers used in the study.
2. There was no significant association between the presence of d-OIPN and CPT (CPT 2000Hz, CPT 250Hz and CPT 5Hz). Therefore, in this sample, CPT at 2000Hz, 250Hz and 5Hz, did not vary by OIPN status.
3. In this sample, although participants experienced new onset and worsening OIPN-NP with d-OIPN, which persisted through the end of oxaliplatin treatment, there was no significant association between OIPN-NP and OIPN.
4. In this sample, OIPN did not have any significant association with QoL. OIPN-NP (NPS scores) on the other hand was independently associated with QoL and this association is significant.

CHAPTER 5

DISCUSSION, LIMITATIONS AND RECOMMENDATIONS

5.1. Introduction

This chapter includes a summary of the study, the study results, and a discussion of these results within the context of the current literature. Limitations of the study and recommendations for future studies will also be discussed.

5.2. Study Overview

This study was designed to assess sensory fiber function in patients who may develop peripheral neuropathy after receiving chemotherapy. Specifically, the purpose was to explore the role of CPT in assessing OIPN in patients receiving oxaliplatin-based chemotherapy, by comparing the performance of CPT with established QST measures. CPT is unique in that it is easier to use than NCS and QST and can assess large Aβ and small Aδ and C fibers. The second purpose of this study was to examine the relationship between OIPN and OIPN-NP and to determine if OIPN-NP independently influenced QoL. The relationships between the variables in the study were organized around a conceptual framework, guided by the Neuromatrix Theory of Pain.

This study was a secondary data analysis of data from a prospective, longitudinal, descriptive study, designed to characterize the development of OIPN. As such, a correlational, descriptive design was used to guide this analysis. The study included a total of 19 participants of which data from 18 participants was available for analysis. Assessments were performed and data collected on participants prior to receiving chemotherapy (baseline), after receiving 500mg/m2 of oxaliplatin (midpoint) and after

completing treatment. Of the 19 participants, 10 were assessed at midpoint and 9 were available for assessment after treatment completion.

5.3. Association between CPT and QST in the setting of d-OIPN

Participants in this study presented with symptoms of OIPN that were consistent with those described in the literature and summarized in Table 2. Participants experienced an increase in MDT and a decrease in VPT over the course of oxaliplatin treatment which suggests that large myelinated Aβ fibers were affected. Also, there was a decrease in HPT and an increase in cold pain threshold, indicating that C-fibers were also affected.

CPT 2000Hz had significant associations with MDT and VPT, which are both corresponding QST measures of Aβ fiber function. Increase in the amount of current required to stimulate Aβ fibers at 2000Hz corresponded with increase in MDT and decrease in VPT, reflecting deterioration of Aβ fiber function. CPT 250Hz did not have any association with any of the corresponding QST measure of Aδ fiber function (pin sense and CDT) and CPT 5Hz did not have any association with corresponding QST measure of C fiber function (WDT). The lack of association between CPT 250Hz and CPT 5Hz and their corresponding QST measures may be due to the small sample size of this study. Interestingly, CPT 2000Hz and CPT 250Hz both had significant associations with WDT, which is a measure of C fiber function, whereas CPT 5Hz did not. These findings suggest that at a frequency of 2000Hz, CPT assesses both Aβ and C fibers and at a frequency of 250Hz, CPT assesses C fibers.

An advantage of CPT over QST is its neuro-selective property and the opportunity this provides to exclusively and selectively stimulate specific sensory fibers

without activating others, yet this appears not to be the case in this study. In fact, the usefulness of CPT is premised upon its neuro-selective property. Whereas small sample size may have contributed to the lack of association between CPT 5 and its corresponding QST measure, the significant associations between CPT 2000Hz and CPT 250Hz with WDT call into question, the ability of CPT to selectively and accurately assess sensory fiber damage in the setting of d-OIPN. The inability of CPT to achieve neuro-selectivity in the setting of CIPN has also been previously reported [214]. In that small exploratory study (n = 35) evaluating the role of CPT for assessment of CIPN, CPT 2000Hz (Aβ) and CPT 5Hz (C) had significant associations with CDT (Aδ).

In studies where QST has been used to assess pain state, stimuli which typically activate Aβ fibers may also activate sensitized Aδ- and C fibers. In addition stimuli which are known to activate Aδ fibers may also activate sensitized C fibers. [215–219] The persistence of d-OIPN and OIPN-NP in the study participants suggest the presence of peripheral sensitization. Consequently, it is not surprising that MDT(Aβ), VPT(Aβ) and WDT(C), were associated with a CPT 2000Hz(Aβ) or for WDT(C) to be associated with CPT 250(Aδ). However, QST requires activation of the receptors on sensory nerve endings to stimulate the nerve, whereas CPT bypasses the receptors and directly stimulates the sensory nerves, using electrical current. Since receptors on sensory nerve endings are polymodal in nature, the ability to bypass them and exclusively stimulate specific sensory nerves, in part, confers neuro-selectivity on CPT. It remains to be seen however, whether peripheral sensitization produces the same effects on CPT assessments of sensory fibers as it does on QST assessments.

5.4. Role of QST for assessing d-OIPN

In this study, most of the participants available for assessment at the end of the study had developed d-OIPN. Somatosensory abnormalities associated with d-OIPN include increased MDT, increased VPT and increased cold pain threshold among others. Among the QST measures used in this study, VPT (Aβ) and not MDT (Aβ) was significantly associated with the development of d-OIPN (Table A5). Pin sense (Aδ) was also significantly associated with OIPN. Pin sense and VPT have been reported previously as reliable measures of CIPN in general [13,94]. For this reason, they are commonly used in the research and clinical settings as part of comprehensive physical examinations and are incorporated into composite scales like the TNSc©. Although Aβ and C fibers seem to be most affected in the setting of d-OIPN, decreased pin sense (Aδ) has also been reported during d-OIPN. The somatosensory effects of d-OIPN on C fiber function, typically present as increase in cold pain threshold (C), with or without an increase in WDT (C) [44,62,63]. Notably, there was no association between cold pain threshold and d-OIPN in this study.

It is possible that the lack of association between d-OIPN and cold pain threshold as well as MDT in this study may be attributable to small sample size. Multiple examiners with varied experience levels were also involved in both NCI-CTC and QST assessments and as reported in section 2.2.8(a), there is considerable variation in the inter-rater reliability of the NCI-CTC scale, ranging for 45.9% to 75% [75,96]. Therefore, QST examiner experience as well as inter-rater reliability of NCI-CTC assessments may have also influenced the study results. Unfortunately, there were no records of inter-rater reliability assessments for either NCI-CTC or QST assessments during the primary study.

Future studies should include standardized training for both QST and NCI-CTC assessments to reduce measurement bias.

5.5. Role of CPT for assessing d-OIPN

There was no association between d-OIPN as assessed by NCI-CTC and CPT 2000Hz, CPT 250Hz or CPT 5Hz in this study. Only 9 participants were available for assessment at study conclusion and only 6 of them had developed d-OIPN. Therefore, few participants remained for the entire study duration to allow time for OIPN development. The lack of association between CPT and d-OIPN may therefore have been due to the small and inadequate sample size, evidenced by insufficient observed statistical power. The power of a statistical analysis refers to the probability that the analysis correctly rejects the null hypothesis or reports an association if one exists. Assuming the same study design and analysis, post-hoc analysis showed that to detect a large effect size in CPT at 0.8 power, a sample size of about 125 participants was required.

In addition to the variable inter-reliability of the NCI-CTC discussed previously, another reason for the lack of association between CPT and d-OIPN may also have been the fact that the NCI-CTC scale was not sensitive enough to pick up d-OIPN, especially in the early stages [75,83]. Larger, well-powered, prospective studies utilizing tools like the TNSc© which are more sensitivity to d-OIPN are needed, to conclusively demonstrate any role CPT may play in the assessment of OIPN.

5.6. Relationship between d-OIPN, OIPN-NP and QoL

D-OIPN is often associated with OIPN-NP and has a negative effect on QoL. In this study, there was no relationship between d-OIPN and OIPN-NP, although more

participants developed d-OIPN, experienced higher cold pain thresholds and reported higher NPS scores at the end of treatment compared to baseline and midpoint. D-OIPN is typically not associated with changes in HPT [44,62]. This may be due to degenerative processes in the peripheral nerves such as Wallerian degeneration where damaged sensory nerves begin to degenerate distal to the point of injury, resulting in hypoesthesia or reduced sensation to stimuli. However, several studies have reported an association between d-OIPN and increased cold pain threshold. The small sample size in this study may be a reason for the lack of association between d-OIPN and OIPN-NP (NPS and cold pain threshold), as evidenced insufficient statistical power from post-hoc power analysis for the respective models. Assuming the same study design and analysis, post-hoc analysis showed that to detect a large effect size in cold pain threshold and NPS scores at 0.8 power, a sample size of about 70 and 25 participants respectively, was required. Since, the NPS was introduced after the primary study was well under way, only a subset of the original sample completed this measure. Further, some participants were only able to complete the NPS assessment at midpoint and/or end of study and not at baseline, potentially contributing to the contradictory results obtained see in this study.

Although there is increasing evidence in the literature that d-OIPN is associated with decrease in QoL, no association was found between d-OIPN and QoL in this study. Quality of life assessment in clinical oncology, comprises of several components which can make it a stable construct to measure. Consequently, more frequent assessments, over a longer period, in larger sample sizes, may be needed to detect small effect changes. As illustrated in Figure 6, there was minimal variation in FACT-G scores, particularly after the second assessment time point (after receiving 500mg/m^2 of oxaliplatin). Some

possible reasons for this include that participants may have developed sufficient coping mechanisms and/or possess good support systems which allow them to cope with their diagnoses, treatment and resultant OIPN or participants may have just become used to OIPN symptoms, such that it no longer significantly influences their QoL. They may also be hopeful about the outcome of their treatment, leading to a positive outlook and better QoL.

The fact that participants were assessed only three times over the course of their treatment and the small sample size, evidenced by insufficient statistical power from post-hoc power analysis, may have contributed the lack of association between d-OIPN and QoL in this study. Assuming the same study design and analysis, post-hoc analysis showed that to detect a large effect size in FACT-G scores at 0.8 power, a sample size of about 1500 participants was required. Additionally, the FACT-G assesses the general QoL in patients with cancer, therefore it is possible that this instrument was not sensitive enough to pick up variations in QoL that may have resulted from the presence of OIPN.[153]

There was a significant association between patient-reported OIPN-NP (NPS scores) and QoL explaining 7.3% of the variance in QoL. However, the association was positive, such that as NPS scores increased so did QOL. This finding contradicts previously published studies showing a negative influence of OIPN-NP on QoL. Several reasons could have accounted for these findings. Careful examination of the data revealed that participants who did not have d-OIPN, had higher baseline NPS scores (not associated with OIPN) and reported higher NPS scores at midpoint and end of treatment, compared to those who had d-OIPN. In addition, patients with colorectal cancers have

been reported to have higher levels of NP compared to other cancers [161]. The higher NPS scores among participants without OIPN could be because most of the participants had advanced stages of cancer and had undergone surgery. The pain reported could therefore be due to post-operative pain or pain associated with cancer and unrelated to oxaliplatin. Additionally, participants with NP reported higher QoL (higher median FACT-G scores) throughout the study, compared to those who did not have NP. It is possible that participants who presented with NP were adequately coping with it or had become used to the pain such that it now had minimal effect on the quality of their lives.

5.7. Strengths, limitations and recommendations for future studies

A strength of this study includes the fact that the study sample in the original study was homogeneous. All participants had cancer of the gastrointestinal tract and were receiving oxaliplatin as the only neurotoxic drug. The design in the primary study and the exclusion of participants with pre-existing neuropathy of any source, helped reduce possible factors that could confound the results of the study.

Since this study is a secondary data analysis, the data were not originally collected to answer some of the study questions. To address this, a theoretical framework was adopted to help guide the analysis and interpretation of the data. Missing data was present in this secondary dataset. However, this was due to participant dropout or the late introduction of the NPS in the primary study. As a result, some participants completed the study with NP assessment done only at the end of treatment, resulting in only 6 participants with complete NPS scores at all time points. The problem of missing data is also compounded by the fact that the primary study had a longitudinal design, which

lends itself to missing data. Future studies should include efforts to obtain and administer all measures at all assessment time points to minimize missing data.

The small sample size in this study constitutes the major limitation of this study. Small sample size reduces statistical power and therefore may influence the accuracy and generalizability of the study findings. To address the issue of missing data and small sample size, LMM were adopted for data analysis. This technique takes advantage of the strength of longitudinal designs, including repeated measurement of the same phenomenon over time. The LMM approach is therefore very robust and uses all available data points to provide parameter estimates in datasets with small sample sizes containing missing data. This is an advantage over methods like repeated measures ANOVA, which eliminates whole data points that may contain missing data, thus reducing sample size.

Attrition was also a limitation in this study. By the third assessment time point, about half of the study participants had dropped out of the study. Recruiting participants for cancer studies can be difficult, since patients may consider participation an additional burden to the stress of diagnosis and treatment. Attrition in studies involving cancer patients tend to be high as participants can develop complications from the primary cancer or the treatment course, making them ineligible or physically unable to continue participation in the study.

The presence of potentially confounding factors also pose a challenge to the interpretation of results. Participants who had pain at baseline were recruited into the study. This posed a problem in determining whether pain experienced in the study was due to oxaliplatin administration or worsening pre-existing pain, unrelated to oxaliplatin

treatment. Additionally, the NPS was introduced after the study was well underway, leading to missing data. To address these problems, future studies should increase the pool of potential participants by recruiting from multiple sites and efforts should be made to ensure that valid and reliable tools are ready and available for all study assessments at all assessment time points to reduce minimize the likelihood of missing data. Finally, relevant inclusion/exclusion criteria as well as proper screening should be done to ensure that participants do not have any baseline characteristics (e.g. pain at baseline), that may present challenges to interpretation of results.

Another limitation of this study is that different staff members performed assessments on the same participants at different time points during the primary study, thus creating the possibility of measurement error or bias, especially with QST, where tester consistency is important to obtain consistent results. Future studies should include standardized training and inter-rater reliability testing to document consistency of test administration and scoring.

Although the NCI-CTC is the most commonly used instrument for grading OIPN, it still lacks the ability to assess sensory fiber function and has been shown to under-report cases of chemotherapy-induced neurotoxicity, compared to the TNSc©, which includes sensory nerve fiber assessments. [83] Other limitations of the NCI-CTC are discussed in section 2.2.8. Future studies should include better instruments like the TNSc© which have been shown to be superior to the NCI-CTC in assessing and classifying CIPN and more sensitive QoL instruments like the FACT/GOG-Ntx, which specifically target the influence of CIPN QoL.

5.8. Implications for practice and research

This study supports the current evidence that VPT and pin sense remain good tools for the assessment of OIPN. There is growing consensus that the best instruments for assessing CIPN may be composite instruments, which include patient report and detailed physical assessment including the use of QST measures like vibration perception and pin sense [94,96]. CPT holds potential value in this regard because it has the potential to be able to neuroselectively assess sensory fibers in the setting of CIPN. CPT at 2000Hz is significantly associated with MDT and VPT and can be utilized for assessment of Aβ fiber function in d-OIPN setting. More studies are needed to provide better understanding of the how peripheral sensitization might influence the neuro-selective properties of CPT in the assessment of sensory fibers in the setting of OIPN. More studies are also needed to determine if CPT can discriminate between patients who develop OIPN those who do not. These studies should be large, well-powered prospective studies, which control for confounding factors, reducing measurement errors or bias and increase inter-rater reliability through training. These studies should also utilize better CIPN assessment tools like the TNS© to improve the accuracy of CIPN diagnosis and allow for better assessment of CPT capabilities.

OIPN is associated with NP and this has a negative effect on QoL. The possibility exists that OIPN-NP influences QoL, independent of the effects of OIPN. To address the association between OIPN-NP and d-OIPN, future studies should include proper screening to ensure that participants do not have any pain at baseline. Further, NP assessments should be performed at all assessment time points using valid and reliable

pain tools. This will reduce confounding factors which may complicate the interpretation of study findings.

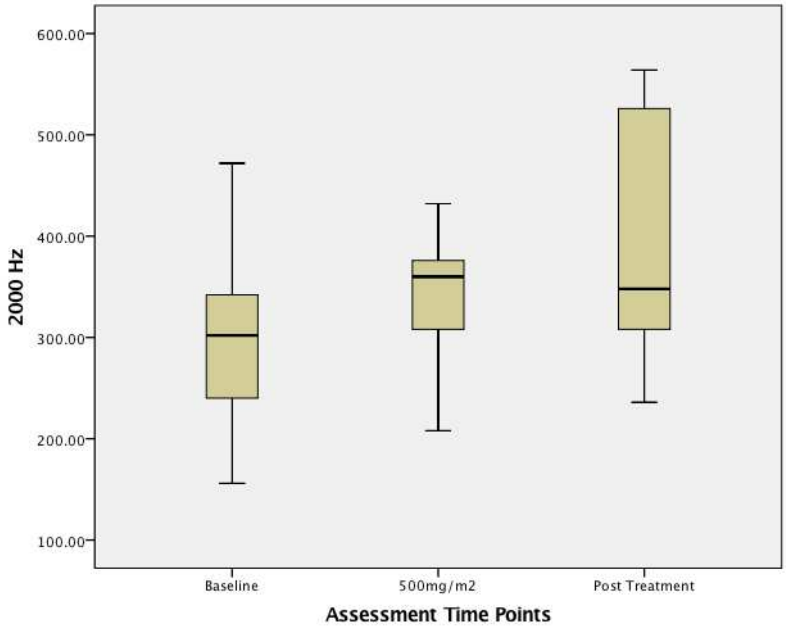
Clinically, it is therefore important to vigilantly assess for the presence of NP in patients who receive oxaliplatin using valid and reliable pain instruments such as the NPS. Adequate pain management should also be incorporated into the care plan for these patients to improve their QoL.

5.9. Summary

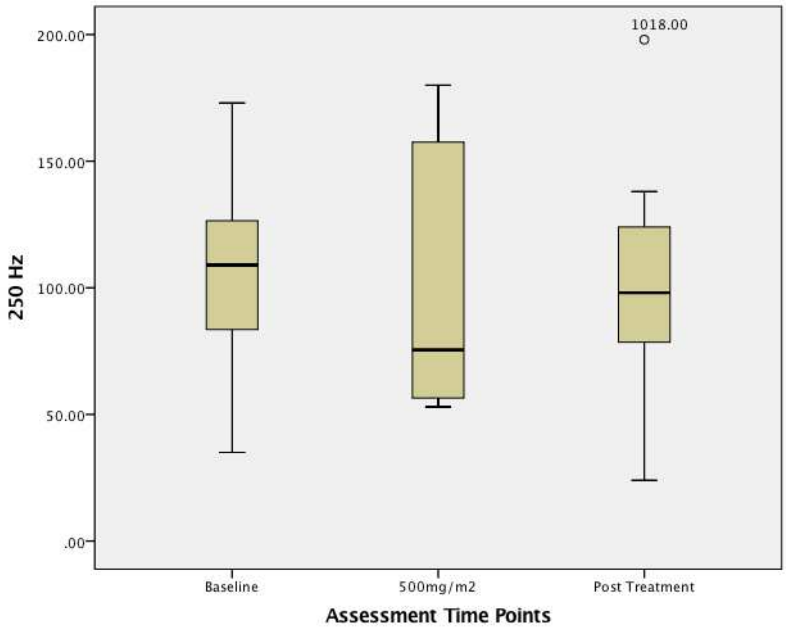
Much work remains to be done to develop valid and reliable instruments that can be easily used for the assessment of sensory fiber function in the setting of OIPN. This is imperative in order to be able to accurately estimate the scope of the problem, better understand the mechanisms associated with OIPN and monitor the progression of OIPN as well as its response to treatment. Although CPT 2000Hz was associated with VPT and MDT, it did not demonstrate sufficient neuro-selectivity. The value of CPT for the assessment of OIPN is therefore inconclusive and further studies are needed to conclusively determine the role of CPT for the assessment of OIPN. NP is a unique and different problem associated with OIPN and it affects QoL. Efforts need to be made to incorporate pain assessments and interventions to address this problem in patients who develop OIPN.

APPENDIX

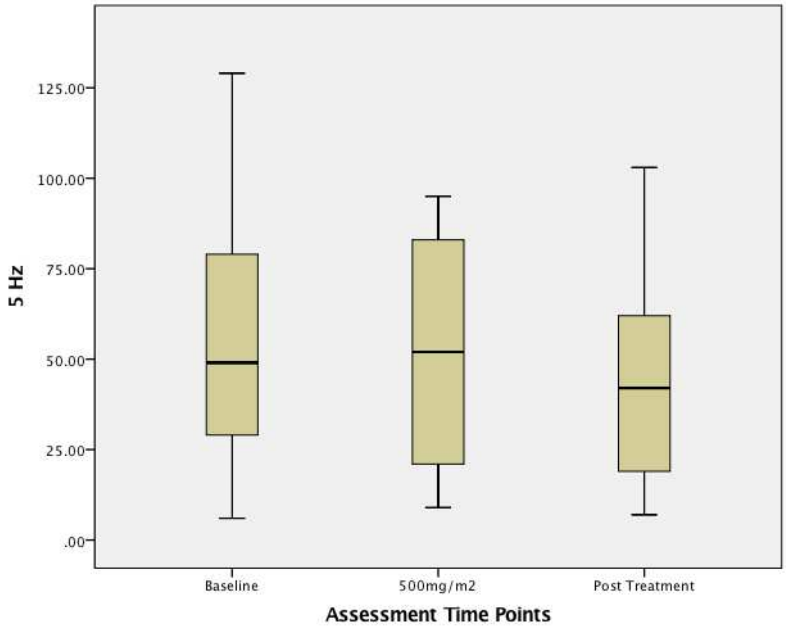
Appendix A1: CPT 2000Hz over time



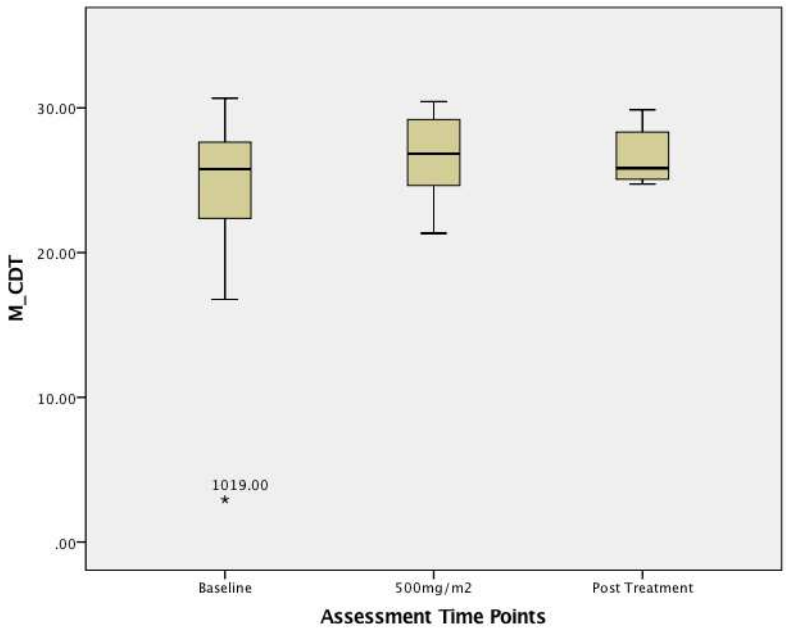
Appendix A2: CPT 250Hz over time



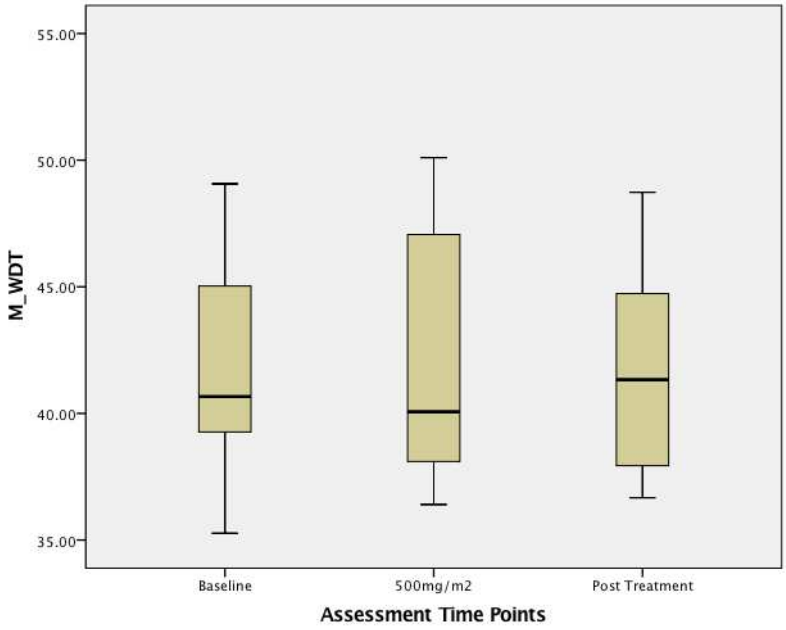
Appendix A3: CPT 5 over time



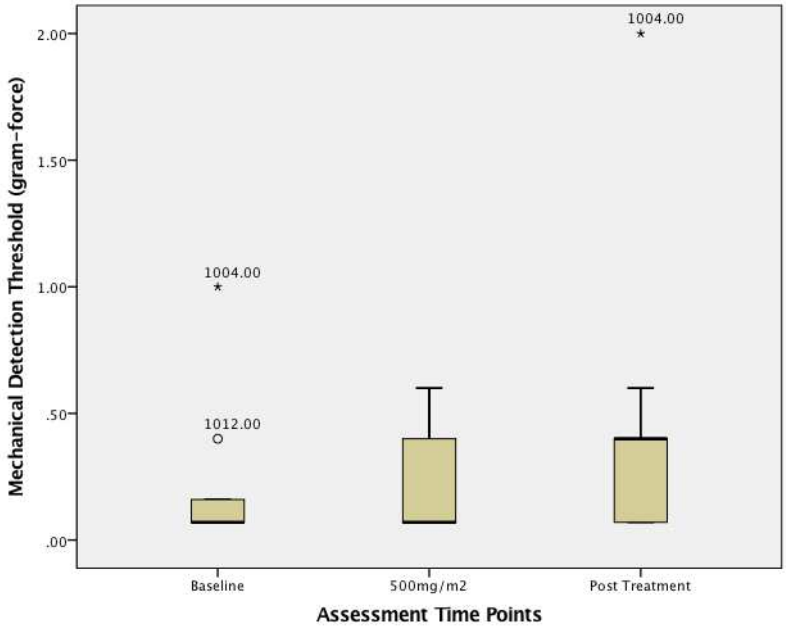
Appendix A4: Cold detection threshold over time



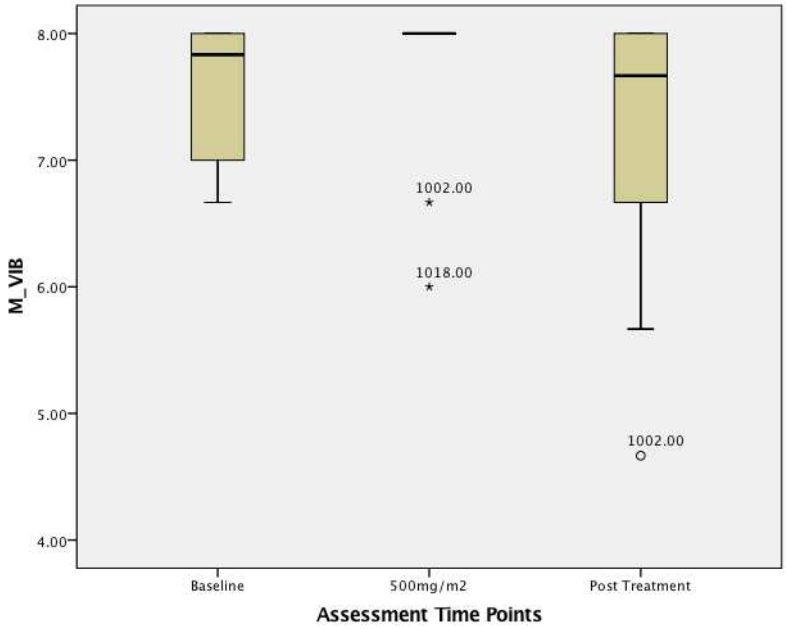
Appendix A5: Warm detection threshold over time



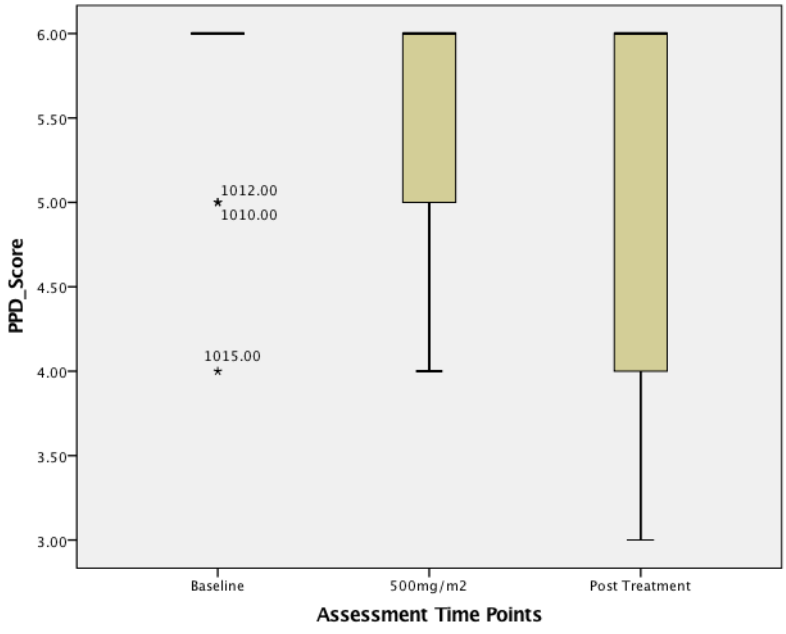
Appendix A6: Mechanical detection threshold over time



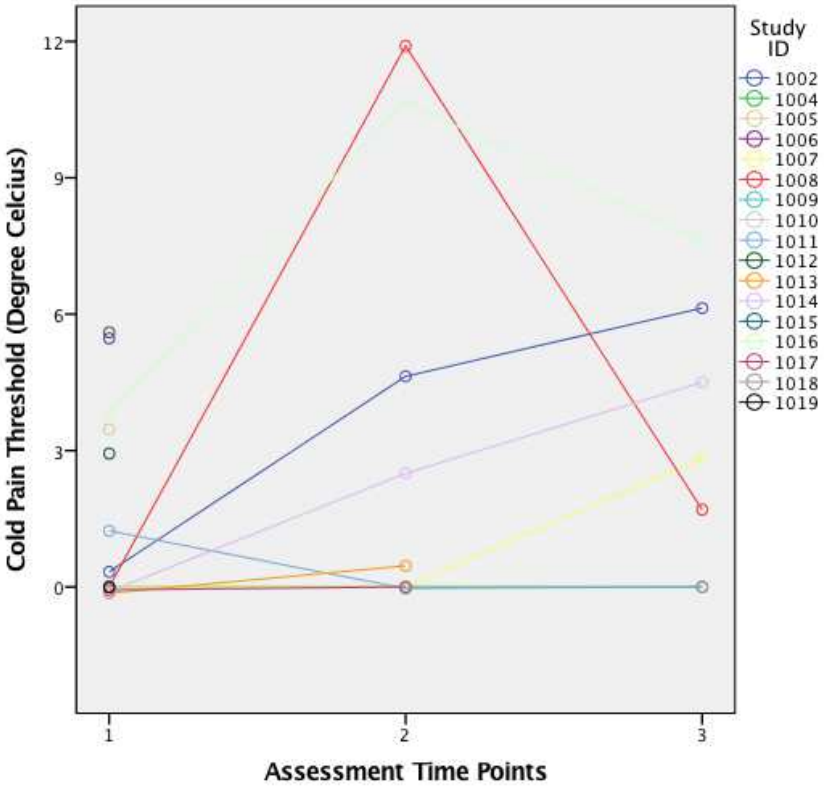
Appendix A7: Vibration detection threshold over time



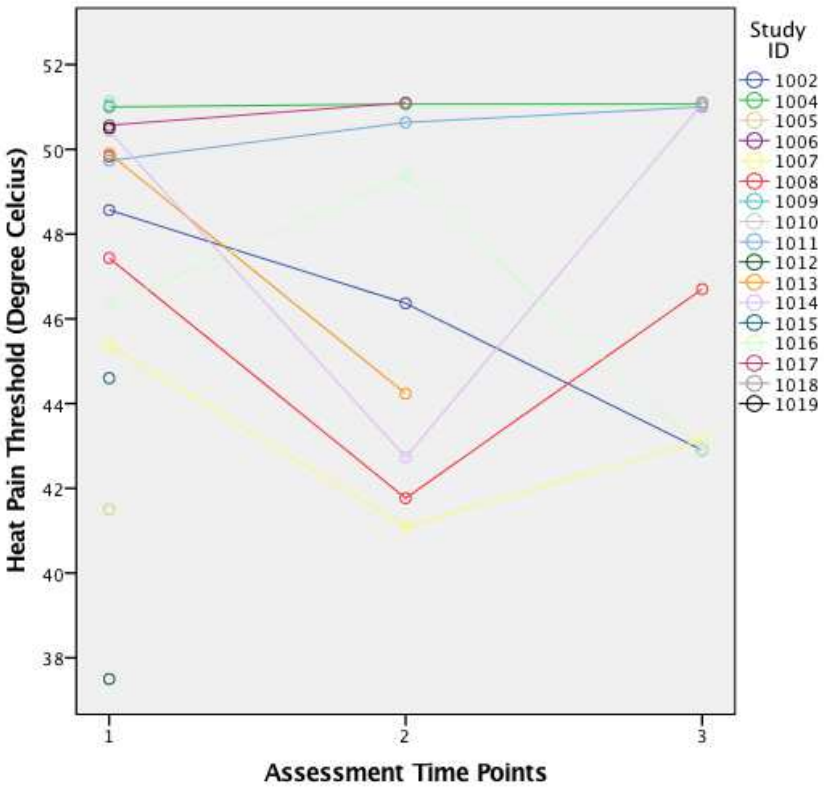
Appendix A8: Pin sense scores over time



Appendix B1: Spaghetti plot for cold pain threshold



Appendix B2: Spaghetti plot for mean heat pain threshold



Appendix B3: Spaghetti plot for Neuropathic Pain Scale scores

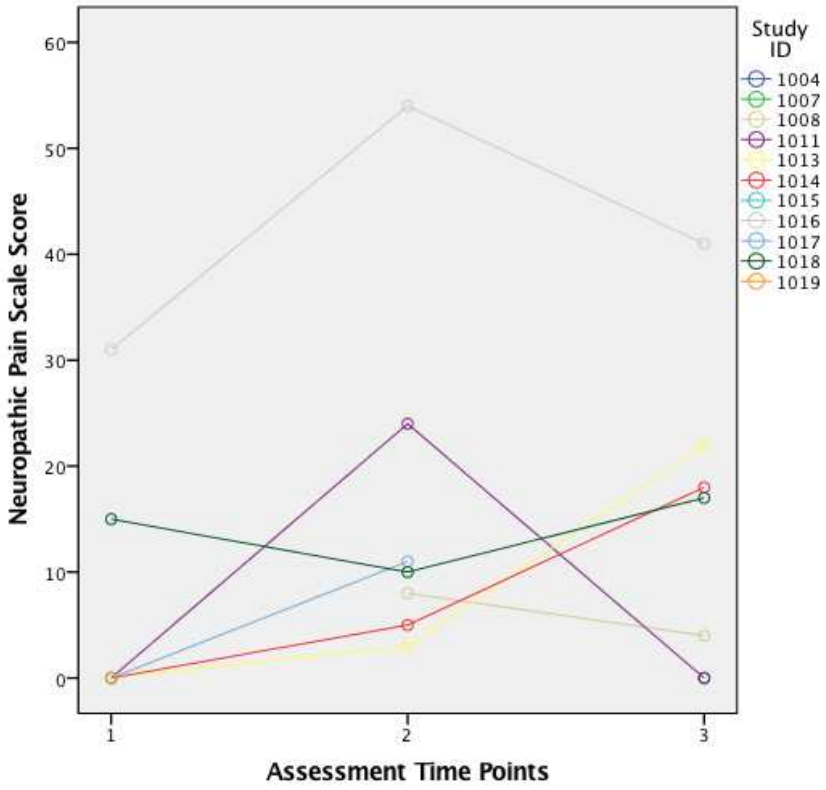


Table A1: Descriptive analysis of NPS scores by OIPN status

Statistic	Baseline		500mg/m2		End of Treatment	
	OIPN	No OIPN	OIPN	No OIPN	OIPN	No OIPN
N	0	8	3	4	5	3
Minimum	0	0	5	3	0	4
Maximum	0	31	11	54	18	41
Mean (SD)	0	5.8(11.5)	8.7(3.2)	22.3(22.9)	7.0(9.6)	22.3(18.5)
Median	0	0	10	16	0	22
Range	0	31	6	51	18	37

Table A2: Descriptive analysis of cold pain threshold by OIPN status

Statistic	Baseline		500mg/m2		End of Treatment	
	OIPN	No OIPN	OIPN	No OIPN	OIPN	No OIPN
N	0	16	2	7	6	2
Minimum	0	-0.13	0	-0.03	0	1.7
Maximum	0	5.6	2.5	11.9	6.3	7.6
Mean (SD)	0	1.4(2.1)	1.3(1.8)	3.9(5.3)	2.2(2.7)	4.7(4.2)
Median	0	0	1.3	0.5	1.4	4.7
Range	0	5.7	2.5	11.9	6.1	5.9

Table A3: Descriptive analysis of heat pain threshold by OIPN status

Statistic	Baseline		500mg/m2		End of Treatment	
	OIPN	No OIPN	OIPN	No OIPN	OIPN	No OIPN
N	0	16	2	7	6	2
Minimum	0	37.5	42.7	41.1	42.9	42.9
Maximum	0	51.1	51.1	51.1	51.1	46.7
Mean (SD)	0	47.8(3.9)	46.9(5.9)	46.4(4.1)	48.4(4.2)	44.8(2.7)
Median	0	49.8	46.9	46.4	51	44.8
Range	0	13.6	8.4	9.9	8.2	3.8

Table A4: Descriptive analysis of FACT-G scores by OIPN status

Statistic	Baseline		500mg/m2		End of Treatment	
	OIPN	No OIPN	OIPN	No OIPN	OIPN	No OIPN
N	0	18	3	7	5	3
Minimum	0	37	38	28	33	46.8
Maximum	0	63	65	68	66	64.3
Mean (SD)	0	49.8(7.2)	55.6(15.3)	46.7(14.1)	46.9(12.2)	56.7(8.9)
Median	0	49.5	64	48.3	46	59
Range	0	26	27	40	33	17.5

Table A5: Bivariate association between OIPN (predictor) and QST measures (outcome)

QST Measures	Parameter estimates for QST Measures		
	β (SE)	p-value	CI
Mechanical detection threshold	0.08 (0.11)	0.469	-0.1487 – 0.3127
Pin Sense	-0.56 (0.26)	0.042	-1.0993 – -0.0215
Vibration perception Threshold	-0.61 (0.24)	0.020	-1.1107 – -0.1027
Cold detection threshold	-2.22(1.68)	0.202	-5.7439 – 1.3023
Warm Detection threshold	0.39 (1.77)	0.803	-3.3281 – 4.0995

Table A6: Variables included in descriptive analysis.

Variables	Method of Measurement	Level of Measurement
Demographic Factors		
Gender	Male/Female	Nominal
Age	Years	Scale
Race	6 categories	Nominal
Level of Education	6 levels	Ordinal
Physiological Factors		
Weight	Kg	Scale
Height	cm	Scale
Body Surface Area (BSA)	m^2	Scale
Body Mass Index (BMI)	Kg/m^2	Scale
Clinical Factors		
Cancer Diagnosis	13 diagnoses	Nominal
Cancer Stage	4 stages	Nominal
Type of current cancer treatment	3 types	Nominal
Past Cancer Treatment	4 types	Nominal
Concurrent Cancer Treatment	4 categories	Nominal
Surgical Resection of Tumor	Yes or No	Nominal
Chemotherapy Regimen	7 regimens	Nominal
Oxaliplatin dose/cycle	mg/m^2	Ordinal
Oxaliplatin dose at $500mg/m^2$	mg	Scale
Cumulative Oxaliplatin dose	mg	Scale
Baseline to $500mg/m^2$ of oxaliplatin*	Weeks	Scale
$500mg/m^2$ to end of treatment*	Weeks	Scale
Number of chemotherapy cycles	N/A	Scale

Table A7: Variables included in multivariate analysis

Variables	Unit of Measurement	Level of Measurement	Predictor/ Outcome
Measures			
Current perception threshold (CPT)			
- 2000Hz	mA	Scale	Predictor
- 250Hz	mA	Scale	Predictor
- 5Hz	mA	Scale	Predictor
CPT test duration	Minutes	Scale	Covariate
Quantitative Sensory Testing (QST)			
- WDT	°C	Scale	Predictor
- CDT	°C	Scale	Predictor
- HPT	°C	Scale	Predictor
- Cold pain threshold	°C	Scale	Predictor
MDT	gm	Scale	Predictor
VDT	0-8	Scale	Predictor
Pin Sense		Scale	Predictor
NCI-CTC grade		Scale	Predictor
- Peripheral sensory neuropathy	0-5	Ordinal	Outcome
- Paresthesia	0-5	Ordinal	Outcome
- Neuralgia	0-5	Ordinal	Outcome
FACT-G score	0-108	Scale	Outcome
Neuropathy Pain Scale	0-10		
- Items 1 – 10		Scale	Outcome

References

1. André T, Bensmaine MA, Louvet C, et al. Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. *J Clin Oncol*. 1999;17(11):3560-3568. http://www.ncbi.nlm.nih.gov/pubmed/10550155. Accessed December 3, 2014.
2. de Gramont A, Banzi M, Navarro M, et al. Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized mosaic trial. *Proc Am Soc Clin Oncol*. 2003;22(10):151. www.asco.org/ac/1,1003,_12-002489-00_18-002003-00_19-00102693-00_29-00A,00.asp.
3. Comella P, Lorusso V, Maiorino L, et al. Oxaliplatin, irinotecan, and fluorouracil/folinic acid in advanced gastric cancer: a multicenter phase II trial of the Southern Italy Cooperative Oncology Group. *Cancer Chemother Pharmacol*. 2009;64(5):893-899. doi:10.1007/s00280-009-0938-4.
4. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18(16):2938-2947. http://www.ncbi.nlm.nih.gov/pubmed/10944126. Accessed August 15, 2014.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30. doi:10.3322/caac.21332.
6. American Cancer Society. Cancer treatment & survivorship: facts & figures 2014-2015. 2015. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-042801.pdf.
7. Kim DY, Kim JH, Lee S-H, et al. Phase II study of oxaliplatin , 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer. *Ann Oncol*. 2003;14(3):383-387. doi:10.1093/annonc/mdg106.
8. Scagliotti G V, Kortsik C, Dark GG, et al. Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: a multicenter, randomized, phase II trial. *Clin Cancer Res*. 2005;11(2 Pt 1):690-696. http://www.ncbi.nlm.nih.gov/pubmed/15701857.
9. Nicoletto MO, Falci C, Pianalto D, et al. Phase II study of pegylated liposomal doxorubicin and oxaliplatin in relapsed advanced ovarian cancer. *Gynecol Oncol*. 2006;100:318-323. doi:10.1016/j.ygyno.2005.08.020.
10. Raymond E, Banquet-Fagot C, Djelloul S, et al. Antitumor activity of oxaliplatin in combination with 5-fluorouracil and thymidylate synthase inhibitor AG337 in human colon, breast and ovarian cancers. *Anticancer Drugs*. 1997;8(9):876-885.
11. Gamelin E, Gamelin L, Bossi L, Quasthoff S. Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. *Semin Oncol*. 2002;29(5 Suppl 15):21-33. doi:10.1053/sonc.2002.35525.
12. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol*. 2000;18(1):136-147. doi:papers://4253D9C4-4004-42F3-8ABE-9698C59DDEF8/Paper/p1473.

13. Padman S, Lee J, Kumar R, et al. Late effects of oxaliplatin-induced peripheral neuropathy (LEON)—cross-sectional cohort study of patients with colorectal cancer surviving at least 2 years. *Support Care Cancer*. 2015;23(3):861-869. doi:10.1007/s00520-014-2423-9.
14. Pachman DR, Qin R, Seisler DK, et al. Clinical Course of Oxaliplatin-Induced Neuropathy: Results From the Randomized Phase III Trial N08CB (Alliance). *J Clin Oncol*. 2015;33(30):3416-3422. doi:10.1200/JCO.2014.58.8533.
15. Tofthagen C, Donovan KA, Morgan MA, Shibata D, Yeh Y. Oxaliplatin-induced peripheral neuropathy's effects on health-related quality of life of colorectal cancer survivors. *Support Care Cancer*. 2013;21(12):3307-3313. doi:10.1007/s00520-013-1905-5.
16. Attal N, Bouhassira D, Gautron M, et al. Thermal hyperalgesia as a marker of oxaliplatin neurotoxicity: a prospective quantified sensory assessment study. *Pain*. 2009;144(3):245-252. doi:10.1016/j.pain.2009.03.024.
17. Altaf R, Lund Brixen A, Kristensen B, Nielsen SE. Incidence of Cold-Induced Peripheral Neuropathy and Dose Modification of Adjuvant Oxaliplatin-Based Chemotherapy for Patients with Colorectal Cancer. *Oncology*. 2014;87(3):167-172. doi:10.1159/000362668.
18. Argyriou AA, Cavaletti G, Briani C, et al. Clinical pattern and associations of oxaliplatin acute neurotoxicity: A prospective study in 170 patients with colorectal cancer. *Cancer*. 2013;119(2):438-444. doi:10.1002/cncr.27732.
19. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2014;32(18):1941-1967. doi:10.1200/JCO.2013.54.0914.
20. Balayssac D, Ferrier J, Descoeur J, et al. Chemotherapy-induced peripheral neuropathies: from clinical relevance to preclinical evidence. *Expert Opin Drug Saf*. 2011;10(3):407-417. doi:10.1517/14740338.2011.543417.
21. Petrioli R, Paolelli L, Marsili S, et al. FOLFOX-4 stop and go and capecitabine maintenance chemotherapy in the treatment of metastatic colorectal cancer. *Oncology*. 2006;70(5):345-350.
22. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer--a GERCOR study. *J Clin Oncol*. 2006;24(3):394-400. doi:10.1200/JCO.2005.03.0106.
23. Petrioli R, Pascucci A, Francini E, et al. Neurotoxicity of FOLFOX-4 as adjuvant treatment for patients with colon and gastric cancer: a randomized study of two different schedules of oxaliplatin. *Cancer Chemother Pharmacol*. 2008;61(1):105-111.
24. Loprinzi CL, Qin R, Dakhil SR, et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). *J Clin Oncol*. 2014;32(10):997-1005. doi:10.1200/JCO.2013.52.0536.
25. Smith EML, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA*. 2013;309(13):1359-1367.

doi:10.1001/jama.2013.2813.
26. Yang Y-H, Lin J-K, Chen W-S, et al. Duloxetine improves oxaliplatin-induced neuropathy in patients with colorectal cancer: an open-label pilot study. *Support Care Cancer*. 2012;20(7):1491-1497. doi:10.1007/s00520-011-1237-2.
27. Argyriou AA, Cavaletti G, Briani C, et al. Clinical pattern and associations of oxaliplatin acute neurotoxicity. *Cancer*. 2013;119(2):438-444. doi:10.1002/cncr.27732.
28. Díaz-Rubio E, Sastre J, Zaniboni A, et al. Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: a phase II multicentric study. *Ann Oncol*. 1998;9(1):105-108. http://www.ncbi.nlm.nih.gov/pubmed/9541691.
29. Briani C, Argyriou AA, Izquierdo C, et al. Long-term course of oxaliplatin-induced polyneuropathy: a prospective 2-year follow-up study. *J Peripher Nerv Syst*. 2014;19(4):299-306. doi:10.1111/jns.12097.
30. Shahriari-Ahmadi A, Fahimi A, Payandeh M, Sadeghi M. Prevalence of Oxaliplatin-induced Chronic Neuropathy and Influencing Factors in Patients with Colorectal Cancer in Iran. *Asian Pac J Cancer Prev*. 2015;16(17):7603-7606. http://www.ncbi.nlm.nih.gov/pubmed/26625769.
31. Xiao WH, Zheng H, Bennett GJ. Characterization of oxaliplatin-induced chronic painful peripheral neuropathy in the rat and comparison with the neuropathy induced by paclitaxel. *Neuroscience*. 2012;203:194-206. doi:10.1016/j.neuroscience.2011.12.023.
32. Velasco R, Bruna J, Briani C, et al. Early predictors of oxaliplatin-induced cumulative neuropathy in colorectal cancer patients. *J Neurol Neurosurg Psychiatry*. 2014;85(4):392-398. doi:10.1136/jnnp-2013-305334.
33. Alejandro LM, Behrendt CE, Chen K, Openshaw H, Shibata S. Predicting Acute and Persistent Neuropathy Associated With Oxaliplatin. *Am J Clin Oncol*. 2013;36(4):331-337. doi:10.1097/COC.0b013e318246b50d.
34. Pachman DR, Barton DL, Watson JC, Loprinzi CL. Chemotherapy-induced peripheral neuropathy: prevention and treatment. *Clin Pharmacol Ther*. 2011;90(3):377-387. doi:10.1038/clpt.2011.115.
35. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain*. 2014;155(12):2461-2470. doi:10.1016/j.pain.2014.09.020.
36. Ramanathan RK, Rothenberg ML, de Gramont A, et al. Incidence and evolution of oxaliplatin-induced peripheral sensory neuropathy in diabetic patients with colorectal cancer: a pooled analysis of three phase III studies. *Ann Oncol*. 2010;21(4):754-758. doi:10.1093/annonc/mdp509.
37. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004;350(23):2343-2351. doi:10.1056/NEJMoa032709.
38. Souglakos J, Mavroudis D, Kakolyris S, et al. Triplet combination with irinotecan plus oxaliplatin plus continuous-infusion fluorouracil and leucovorin as first-line treatment in metastatic colorectal cancer: a multicenter phase II trial. *J Clin Oncol*. 2002;20(11):2651-2657. http://www.ncbi.nlm.nih.gov/pubmed/12039926.
39. Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP. A review on oxaliplatin-induced peripheral nerve damage. *Cancer Treat Rev*.

2008;34(4):368-377. doi:10.1016/j.ctrv.2008.01.003.
40. Nurgalieva Z, Xia R, Liu C-C, Burau K, Hardy D, Du XL. Risk of Chemotherapy-Induced Peripheral Neuropathy in Large Population-Based Cohorts of Elderly Patients With Breast, Ovarian, and Lung Cancer. *Am J Ther*. 2010;17(2):148-158. doi:10.1097/MJT.0b013e3181a3e50b.
41. Beijers AJM, Mols F, Vreugdenhil G. A systematic review on chronic oxaliplatin-induced peripheral neuropathy and the relation with oxaliplatin administration. *Support Care Cancer*. 2014;22(7):1999-2007. doi:10.1007/s00520-014-2242-z.
42. Velasco R, Bruna J. Chemotherapy-induced peripheral neuropathy: an unresolved issue. *Neurologia*. 2010;25(2):116-131.
43. Griffith KA, Couture DJ, Zhu S, et al. Evaluation of chemotherapy-induced peripheral neuropathy using current perception threshold and clinical evaluations. *Support Care Cancer*. 2014;22(5):1161-1169. doi:10.1007/s00520-013-2068-0.
44. Reddy SM, Vergo MT, Paice JA, et al. Quantitative Sensory Testing at Baseline and During Cycle 1 Oxaliplatin Infusion Detects Subclinical Peripheral Neuropathy and Predicts Clinically Overt Chronic Neuropathy in Gastrointestinal Malignancies. *Clin Colorectal Cancer*. 2016;15(1):37-46. doi:10.1016/j.clcc.2015.07.001.
45. Morton RF, Sloan JA, Grothey A, et al. A comparison of simple single-item measures and the common toxicity criteria in detecting the onset of oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer. *J Clin Oncol*. 2005;23(16S (June 1 Supplement)):8087.
46. Atherton PJ, Watkins-Bruner DW, Gotay C, et al. The Complementary Nature of Patient-Reported Outcomes and Adverse Event Reporting in Cooperative Group Oncology Clinical Trials: A Pooled Analysis (NCCTG N0591). *J Pain Symptom Manage*. 2015;50(4):470-479.e9. doi:10.1016/j.jpainsymman.2015.04.016.
47. Burakgazi a Z, Messersmith W, Vaidya D, Hauer P, Hoke A, Polydefkis M. Longitudinal assessment of oxaliplatin-induced neuropathy. *Neurology*. 2011;77(10):980-986. doi:10.1212/WNL.0b013e31822cfc59.
48. Krøigård T, Schrøder HD, Qvortrup C, et al. Characterization and diagnostic evaluation of chronic polyneuropathies induced by oxaliplatin and docetaxel comparing skin biopsy to quantitative sensory testing and nerve conduction studies. *Eur J Neurol*. 2014;21(4):623-629. doi:10.1111/ene.12353.
49. Park S, Krishnan A, Lin C, Goldstein D, Friedlander M, Kiernan M. Mechanisms Underlying Chemotherapy-Induced Neurotoxicity and the Potential for Neuroprotective Strategies. *Curr Med Chem*. 2008;15(29):3081-3094. doi:10.2174/092986708786848569.
50. McKeage MJ, Hsu T, Screnci D, Haddad G, Baguley BC. Nucleolar damage correlates with neurotoxicity induced by different platinum drugs. *Br J Cancer*. 2001;85(8):1219-1225.
51. Jamieson SMF, Liu J, Connor B, McKeage MJ. Oxaliplatin causes selective atrophy of a subpopulation of dorsal root ganglion neurons without inducing cell loss. *Cancer Chemother Pharmacol*. 2005;56(4):391-399. doi:10.1007/s00280-004-0953-4.
52. Kono T, Satomi M, Suno M, et al. Oxaliplatin-induced neurotoxicity involves TRPM8 in the mechanism of acute hypersensitivity to cold sensation. *Brain*

Behav. 2012;2(1):68-73. doi:10.1002/brb3.34.
53. Trevisan G, Materazzi S, Fusi C, et al. Novel therapeutic strategy to prevent chemotherapy-induced persistent sensory neuropathy by TRPA1 blockade. *Cancer Res*. 2013;73(10):3120-3131. doi:10.1158/0008-5472.CAN-12-4370.
54. Krishnan A V, Goldstein D, Friedlander M, Kiernan MC. Oxaliplatin and axonal Na+ channel function in vivo. *Clin Cancer Res*. 2006;12(15):4481-4484.
55. Ferrier J, Pereira V, Busserolles J, Authier N, Balayssac D. Emerging trends in understanding chemotherapy-induced peripheral neuropathy. *Curr Pain Headache Rep*. 2013;17(10):364. doi:10.1007/s11916-013-0364-5.
56. Xiao WH, Bennett GJ. Effects of mitochondrial poisons on the neuropathic pain produced by the chemotherapeutic agents, paclitaxel and oxaliplatin. *Pain*. 2012;153(3):704-709. doi:10.1016/j.pain.2011.12.011.
57. Di Cesare Mannelli L, Zanardelli M, Failli P, Ghelardini C. Oxaliplatin-induced neuropathy: Oxidative Stress as Pathological Mechanism. Protective Effect of Silibinin. *J Pain*. 2012;13(3):276-284. doi:10.1016/j.jpain.2011.11.009.
58. Carozzi VA, Marmiroli P, Cavaletti G. The role of oxidative stress and anti-oxidant treatment in platinum-induced peripheral neurotoxicity. *Curr Cancer Drug Targets*. 2010;10(7):670-682. http://www.ncbi.nlm.nih.gov/pubmed/20578989. Accessed September 11, 2014.
59. Azevedo MI, Pereira AF, Nogueira RB, et al. The antioxidant effects of the flavonoids rutin and quercetin inhibit oxaliplatin-induced chronic painful peripheral neuropathy. *Mol Pain*. 2013;9:53. doi:10.1186/1744-8069-9-53.
60. Treede R-D, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70(18):1630-1635. doi:10.1212/01.wnl.0000282763.29778.59.
61. Merskey, H., Bogduk N. *Classification of Chronic Pain*. 2nd Editio. Seattle, WA: International Association for the Study of Pain; 1994.
62. de Carvalho Barbosa M, Kosturakis AK, Eng C, et al. A Quantitative Sensory Analysis of Peripheral Neuropathy in Colorectal Cancer and Its Exacerbation by Oxaliplatin Chemotherapy. *Cancer Res*. 2014;74(21):5955-5962. doi:10.1158/0008-5472.CAN-14-2060.
63. Binder A, Stengel M, Maag R, et al. Pain in oxaliplatin-induced neuropathy--sensitisation in the peripheral and central nociceptive system. *Eur J Cancer*. 2007;43(18):2658-2663. doi:10.1016/j.ejca.2007.07.030.
64. Wolf SL, Barton DL, Qin R, et al. The relationship between numbness, tingling, and shooting/burning pain in patients with chemotherapy-induced peripheral neuropathy (CIPN) as measured by the EORTC QLQ-CIPN20 instrument, N06CA. *Support Care Cancer*. 2012;20(3):625-632. doi:10.1007/s00520-011-1141-9.
65. Mols F, Beijers T, Lemmens V, van den Hurk CJ, Vreugdenhil G, van de Poll-Franse L V. Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. *J Clin Oncol*. 2013;31(21):2699-2707. doi:10.1200/JCO.2013.49.1514.
66. Jones D, Zhao F, Brell J, et al. Neuropathic symptoms, quality of life, and clinician perception of patient care in medical oncology outpatients with colorectal, breast,

lung, and prostate cancer. *J Cancer Surviv*. 2015;9(1):1-10. doi:10.1007/s11764-014-0379-x.
67. Geber C, Breimhorst M, Burbach B, et al. Pain in chemotherapy-induced neuropathy--more than neuropathic? *Pain*. 2013;154(12):2877-2887. doi:10.1016/j.pain.2013.08.028.
68. Lovie Smith EM, Cohen JA, Pett MA, Beck SL. The reliability and validity of a modified Total Neuropathy Score-reduced when used to measure chemotherapy-induced peripheral neuropathy in patients receiving taxanes and platinums. *Cancer Nurs*. 2010;33(3):173-183.
69. Gill TM, Feinstein AR. A Critical Appraisal of the Quality of Quality-of-Life Measurements. *JAMA J Am Med Assoc*. 1994;272(8):619. doi:10.1001/jama.1994.03520080061045.
70. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11(3):570-579. http://www.ncbi.nlm.nih.gov/pubmed/8445433. Accessed December 2, 2014.
71. Patrick DL, Bergner M. Measurement of health status in the 1990s. *Annu Rev Public Health*. 1990;11:165-183. doi:10.1146/annurev.pu.11.050190.001121.
72. Guyatt GH. Measuring Health-Related Quality of Life. *Ann Intern Med*. 1993;118(8):622. doi:10.7326/0003-4819-118-8-199304150-00009.
73. Postma TJ, Heimans JJ. Grading of Chemotherapy-Induced Peripheral Neuropathy. *Ann Oncol*. 2000;11(5):509-513.
74. Verstappen CCP, Heimans JJ, Hoekman K, Postma TJ. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs*. 2003;63(15):1549-1563. doi:10.2165/00003495-200363150-00003.
75. Postma TJ, Heimans JJ, Muller MJ, Ossenkoppele GJ, Vermorken JB, Aaronson NK. Pitfalls in grading severity of chemotherapy-induced peripheral neuropathy. *Ann Oncol*. 1998;9(7):739-744. doi:10.1023/A:1008344507482.
76. Cavaletti G, Jann S, Pace A, et al. Multi-center assessment of the Total Neuropathy Score for chemotherapy-induced peripheral neurotoxicity. *J Peripher Nerv Syst*. 2006;11(2):135-141. doi:10.1111/j.1085-9489.2006.00078.x.
77. Cavaletti G, Frigeni B, Lanzani F, et al. Chemotherapy-Induced Peripheral Neurotoxicity assessment: a critical revision of the currently available tools. *Eur J Cancer*. 2010;46(3):479-494. doi:10.1016/j.ejca.2009.12.008.
78. Chu SH, Lee YJ, Lee YJ, Cleeland CS. Properties of the Measures to Assess Oxaliplatin-induced Peripheral Neuropathy: A Literature Review. *J Korean Acad Nurs*. 2015;45(6):783. doi:10.4040/jkan.2015.45.6.783.
79. Services H. Common Terminology Criteria for Adverse Events (CTCAE). *Publish*. 2010;2009:0-71. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.
80. Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: The QLQ-CIPN20. *Eur J Cancer*. 2005;41:1135-1139. doi:10.1016/j.ejca.2005.02.012.
81. Huang HQ, Brady MF, Cella D, Fleming G, Mackey D. Validation and reduction

of FACT/GOG-Ntx subscale for platinum/paclitaxel- induced neurologic symptoms: A gynecologic oncology group study. *Int J Gynecol Cancer*. 2007;17:387-393. doi:10.1111/j.1525-1438.2007.00794.x.
82. Cornblath DR, Chaudhry V, Carter K, et al. Total neuropathy score: Validation and reliability study. *Neurology*. 1999;53(8):1660-1660. doi:10.1212/WNL.53.8.1660.
83. Cavaletti G, Frigeni B, Lanzani F, et al. The Total Neuropathy Score as an assessment tool for grading the course of chemotherapy-induced peripheral neurotoxicity: comparison with the National Cancer Institute-Common Toxicity Scale. *J Peripher Nerv Syst*. 2007;12(3):210-215. doi:10.1111/j.1529-8027.2007.00141.x.
84. Smith EML, Beck SL, Cohen J. The total neuropathy score: a tool for measuring chemotherapy-induced peripheral neuropathy. *Oncol Nurs Forum*. 2008;35(1):96-102. doi:10.1188/08.ONF.96-102.
85. Park SB, Goldstein D, Lin CS-Y, Krishnan A V., Friedlander ML, Kiernan MC. Acute abnormalities of sensory nerve function associated with oxaliplatin-induced neurotoxicity. *J Clin Oncol*. 2009;27(8):1243-1249. doi:10.1200/JCO.2008.19.3425.
86. Argyriou AA, Polychronopoulos P, Chroni E. The usefulness of nerve conduction studies in objectively assessing oxaliplatin-induced peripheral neuropathy. *Oncologist*. 2007;12(11):1371-2-3. doi:10.1634/theoncologist.12-11-1371.
87. Dolan C, Bromberg MB. Nerve conduction pitfalls and pearls in the diagnosis of peripheral neuropathies. *Semin Neurol*. 2010;30(4):436-442. doi:10.1055/s-0030-1267288.
88. Burns TM, Taly A, O'Brien PC, Dyck PJ. Clinical versus quantitative vibration assessment: improving clinical performance. *J Peripher Nerv Syst*. 2002;7(2):112-117. doi:10.1046/j.1529-8027.2002.02016.x.
89. Velasco R, Videla S, Villoria J, Ortiz E, Navarro X, Bruna J. Reliability and accuracy of quantitative sensory testing for oxaliplatin-induced neurotoxicity. *Acta Neurol Scand*. 2015;131(5):282-289. doi:10.1111/ane.12331.
90. Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: Clinical and research application in neuropathic pain states. *Pain*. 2007;129(3):256-259. doi:10.1016/j.pain.2007.03.030.
91. Backonja MM, Attal N, Baron R, et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain*. 2013;154(9):1807-1819. doi:10.1016/j.pain.2013.05.047.
92. Lacomis D. Small-fiber neuropathy. *Muscle Nerve*. 2002;26(2):173-188. doi:10.1002/mus.10181.
93. Osmani K, Vignes S, Aissi M, et al. Taxane-induced peripheral neuropathy has good long-term prognosis: a 1- to 13-year evaluation. *J Neurol*. 2012;259(9):1936-1943. doi:10.1007/s00415-012-6442-5.
94. Griffith K a, Dorsey SG, Renn CL, et al. Correspondence between neurophysiological and clinical measurements of chemotherapy-induced peripheral neuropathy: secondary analysis of data from the CI-PeriNomS study. *J Peripher Nerv Syst*. 2014;19(2):127-135. doi:10.1111/jns5.12064.
95. Griffith KA, Merkies ISJ, Hill EE, Cornblath DR. Measures of chemotherapy-

induced peripheral neuropathy: a systematic review of psychometric properties. *J Peripher Nerv Syst*. 2010;15(4):314-325. doi:10.1111/j.1529-8027.2010.00292.x.
96. Cavaletti G, Cornblath DR, Merkies ISJ, et al. The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to the first validity and reliability findings. *Ann Oncol*. 2013;24(2):454-462. doi:10.1093/annonc/mds329.
97. Chong PST, Cros DP. Technology literature review: quantitative sensory testing. *Muscle Nerve*. 2004;29(5):734-747. doi:10.1002/mus.20053.
98. Oishi M, Mochizuki Y, Suzuki Y, et al. Current perception threshold and sympathetic skin response in diabetic and alcoholic polyneuropathies. *Intern Med*. 2002;41(10):819-822. doi:10.2169/internalmedicine.41.819.
99. Katims J. Electrodiagnostic Functional Sensory Evaluation of the Patient with Pain: A Review of the Neuroselective Current Perception Threshold and Pain Tolerance Threshold. *Pain Dig*. 1998;8:219-230.
100. Fujiuchi A, Toga T. Pharmacological effect of capsaicin on rat avoidance behaviours elicited by sine-wave electrical stimulation of different frequencies by Neurometer. *J Pharm Pharmacol*. 2008;60(4):467-471. doi:10.1211/jpp.60.4.0009.
101. Koga K, Furue H, Rashid MH, Takaki A, Katafuchi T, Yoshimura M. Selective activation of primary afferent fibers evaluated by sine-wave electrical stimulation. *Mol Pain*. 2005;1:13. doi:10.1186/1744-8069-1-13.
102. Kiso T, Nagakura Y, Toya T. Neurometer measurement of current stimulus threshold in rats. ... *Pharmacol* ..... 2001;297(1):352-356. http://jpet.aspetjournals.org/content/297/1/352.short. Accessed October 17, 2014.
103. Katims JJ, Naviasky EH, Ng LKY. New screening device for assessment of peripheral neuropathy. *J Occup Med*. 1986;28:1219-1221. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L17229061%5Cnhttp://link.libris.kb.se/sfxkib?sid=EMBASE&issn=00961736&id=doi:&atitle=New+screening+device+for+assessment+of+peripheral+neuropathy&stitle=J.+OCCUP.+MED.&title=Journal+of+Occupational+Medicine&volume=28&issue=12&spage=1219&epage=1221&aulast=Katims&aufirst=J.J.&auinit=J.J.&aufull=Katims+J.J.&coden=JOCMA&isbn=&pages=1219-1221&date=1986&auinit1=J&auinitm=J.
104. Pitei DL, Watkins PJ, Stevens MJ, Edmonds ME. The value of the Neurometer in assessing diabetic neuropathy by measurement of the current perception threshold. *Diabet Med*. 1994;11(9):872-876. http://www.ncbi.nlm.nih.gov/pubmed/7705025. Accessed September 30, 2014.
105. Nather A, Neo SH, Chionh SB, Liew SCF, Sim EY, Chew JLL. Assessment of sensory neuropathy in diabetic patients without diabetic foot problems. *J Diabetes Complications*. 2008;22(2):126-131. doi:10.1016/j.jdiacomp.2006.10.007.
106. Nather A, Keng Lin W, Aziz Z, Hj Ong C, Mc Feng B, B Lin C. Assessment of sensory neuropathy in patients with diabetic foot problems. *Diabet Foot Ankle*. 2011;2:1-5. doi:10.3402/dfa.v2i0.6367.
107. Zheng W, He Y, Chen L. Correlation of current perception threshold and somatosensory evoked potential in diabetes. *Neurophysiol Clin Neurophysiol*. 2012;42(4):241-247. doi:10.1016/j.neucli.2012.02.136.
108. Rendell MS, Katims JJ, Richter R, Rowland F. A comparison of nerve conduction

velocities and current perception thresholds as correlates of clinical severity of diabetic sensory neuropathy. *J Neurol Neurosurg Psychiatry*. 1989;52:502-511. doi:10.1136/jnnp.52.4.502.
109. Tack CJJ, Netten PM, Scheepers MH, Meijer JWG, Smits P, Lutterman J. Comparison of clinical examination, current and vibratory perception threshold in diabetic polyneuropathy. *Neth J Med*. 1994;44:41-49.
110. Nishimura A, Ogura T, Hase H, et al. A correlative electrophysiologic study of nerve fiber involvement in carpal tunnel syndrome using current perception thresholds. *Clin Neurophysiol*. 2004;115:1921-1924. doi:10.1016/j.clinph.2004.03.022.
111. Kang EK, Lim JY, Shin HI, Gong HS, Oh JH, Paik NJ. Comparison between nerve conduction studies and current perception threshold test in carpal tunnel syndrome. *Neurophysiol Clin*. 2008;38:127-131. doi:10.1016/j.neucli.2007.12.003.
112. Doi D, Ota Y, Konishi H, Yoneyama K, Araki T. Evaluation of the Neurotoxicity of Paclitaxel and Carboplatin by Current Perception Threshold in Ovarian Cancer Patients. *J Nippon Med Sch*. 2003;70(2):129-134. doi:10.1272/jnms.70.129.
113. Melzack R. Pain and the neuromatrix in the brain. *J Dent Educ*. 2001;65:1378-1382.
114. Melzack R. Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004. *Pain Pract*. 2005;5(2):85-94. doi:10.1111/j.1533-2500.2005.05203.x.
115. Melzack R. From the gate to the neuromatrix. *Pain*. 1999;Suppl 6:S121-6. doi:10.1016/S0304-3959(99)00145-1.
116. Melzack R. Phantom limbs and the concept of a neuromatrix. *Trends Neurosci*. 1990;13(3):88-92. doi:10.1016/0166-2236(90)90179-E.
117. Raymond E, Faivre S, Chaney S, Woynarowski J, Cvitkovic E. Cellular and molecular pharmacology of oxaliplatin. *Mol Cancer Ther*. 2002;1(3):227-235.
118. Culy CR, Clemett D, Wiseman LR. Oxaliplatin. A review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs*. 2000;60(4):895-924. http://www.ncbi.nlm.nih.gov/pubmed/11085200. Accessed September 11, 2014.
119. Levi F, Metzger G, Massari C, Milano G. Oxaliplatin: pharmacokinetics and chronopharmacological aspects. *Clin Pharmacokinet*. 2000;38(1):1-21.
120. Raymond E, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol*. 1998;9(10):1053-1071.
121. Cvitkovic E, Bekradda M. Oxaliplatin: a new therapeutic option in colorectal cancer. *Semin Oncol*. 1999;26(6):647-662.
122. Argyriou AA, Velasco R, Briani C, et al. Peripheral neurotoxicity of oxaliplatin in combination with 5-fluorouracil (FOLFOX) or capecitabine (XELOX): a prospective evaluation of 150 colorectal cancer patients. *Ann Oncol*. 2012;23(12):3116-3122. doi:10.1093/annonc/mds208.
123. de Gramont a, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18(16):2938-2947. http://www.ncbi.nlm.nih.gov/pubmed/10944126. Accessed August 15, 2014.
124. Pietrangeli A, Leandri M, Terzoli E, Jandolo B, Garufi C. Persistence of High-

Dose Oxaliplatin-Induced Neuropathy at Long-Term Follow-Up. *Eur Neurol*. 2006;56(1):13-16. doi:10.1159/000094376.
125. Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. *Support Care Cancer*. 2014;22(8):2261-2269. doi:10.1007/s00520-014-2255-7.
126. Barton DL, Wos EJ, Qin R, et al. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer*. 2011;19(6):833-841. doi:10.1007/s00520-010-0911-0.
127. Binder A, Stengel M, Maag R, et al. Pain in oxaliplatin-induced neuropathy--sensitisation in the peripheral and central nociceptive system. *Eur J Cancer*. 2007;43(18):2658-2663. doi:10.1016/j.ejca.2007.07.030.
128. Kawashiri T, Egashira N, Kurobe K, et al. L type Ca2+ channel blockers prevent oxaliplatin-induced cold hyperalgesia and TRPM8 overexpression in rats. *Mol Pain*. 2012;8:7. doi:10.1186/1744-8069-8-7.
129. Schulze C, McGowan M, Jordt S-E, Ehrlich BE. Prolonged oxaliplatin exposure alters intracellular calcium signaling: a new mechanism to explain oxaliplatin-associated peripheral neuropathy. *Clin Colorectal Cancer*. 2011;10(2):126-133. doi:10.1016/j.clcc.2011.03.010.
130. Nativi C, Gualdani R, Dragoni E, et al. A TRPA1 antagonist reverts oxaliplatin-induced neuropathic pain. *Sci Rep*. 2013;3:2005. doi:10.1038/srep02005.
131. Zhao M, Isami K, Nakamura S, Shirakawa H, Nakagawa T, Kaneko S. Acute cold hypersensitivity characteristically induced by oxaliplatin is caused by the enhanced responsiveness of TRPA1 in mice. *Mol Pain*. 2012;8:55. doi:10.1186/1744-8069-8-55.
132. Nassini R, Gees M, Harrison S, et al. Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation. *Pain*. 2011;152:1621-1631. doi:10.1016/j.pain.2011.02.051.
133. Sittl R, Lampert A, Huth T, et al. Anticancer drug oxaliplatin induces acute cooling-aggravated neuropathy via sodium channel subtype Na(V)1.6-resurgent and persistent current. *Proc Natl Acad Sci U S A*. 2012;109(17):6704-6709. doi:10.1073/pnas.1118058109.
134. Park SB, Lin CS-Y, Krishnan A V., Goldstein D, Friedlander ML, Kiernan MC. Dose effects of oxaliplatin on persistent and transient Na+ conductances and the development of neurotoxicity. *PLoS One*. 2011;6(4):e18469. doi:10.1371/journal.pone.0018469.
135. Deuis JR, Zimmermann K, Romanovsky AA, et al. An animal model of oxaliplatin-induced cold allodynia reveals a crucial role for Nav1.6 in peripheral pain pathways. *Pain*. 2013;154(9):1749-1757. doi:10.1016/j.pain.2013.05.032.
136. Kagiava A, Tsingotjidou A, Emmanouilides C, Theophilidis G. The effects of oxaliplatin, an anticancer drug, on potassium channels of the peripheral myelinated nerve fibres of the adult rat. *Neurotoxicology*. 2008;29(6):1100-1106. doi:10.1016/j.neuro.2008.09.005.
137. Kagiava A, Kosmidis EK, Theophilidis G. Oxaliplatin-induced hyperexcitation of rat sciatic nerve fibers: An intra-axonal study. *Anticancer Agents Med Chem*. 2013;13(2):373-379. doi:10.2174/1871520611313020023.

138. Dimitrov AG, Dimitrova NA. A possible link of oxaliplatin-induced neuropathy with potassium channel deficit. *Muscle and Nerve*. 2012;45(3):403-411.
139. Descoeur J, Pereira V, Pizzoccaro A, et al. Oxaliplatin-induced cold hypersensitivity is due to remodelling of ion channel expression in nociceptors. *EMBO Mol Med*. 2011;3(5):266-278.
140. Millan MJ. The induction of pain: an integrative review. *Prog Neurobiol*. 1999;57(1):1-164. http://www.ncbi.nlm.nih.gov/pubmed/9987804.
141. Jamieson SMF, Subramaniam J, Liu JJ, et al. Oxaliplatin-induced loss of phosphorylated heavy neurofilament subunit neuronal immunoreactivity in rat DRG tissue. *Mol Pain*. 2009;5:66. doi:10.1186/1744-8069-5-66.
142. Kawashiri T, Egashira N, Watanabe H, et al. Prevention of oxaliplatin-induced mechanical allodynia and neurodegeneration by neurotropin in the rat model. *Eur J Pain*. 2011;15(4):344-350. doi:10.1016/j.ejpain.2010.08.006.
143. Schellingerhout D, LeRoux LG, Hobbs BP, Bredow S. Impairment of Retrograde Neuronal Transport in Oxaliplatin-Induced Neuropathy Demonstrated by Molecular Imaging. *PLoS One*. 2012;7(9):e45776. doi:10.1371/journal.pone.0045776.
144. Sisignano M, Baron R, Scholich K, Geisslinger G. Mechanism-based treatment for chemotherapy-induced peripheral neuropathic pain. *Nat Rev Neurol*. 2014;10(12):694-707. doi:10.1038/nrneurol.2014.211.
145. Blumenthal DT. Assessment of neuropathic pain in cancer patients. *Curr Pain Headache Rep*. 2009;13(4):282-287. doi:10.1007/s11916-009-0045-6.
146. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol*. 2010;9(8):807-819. doi:10.1016/S1474-4422(10)70143-5.
147. Cervero F, Woolf CJ, Owen JEL, Hawley DJ, Wolfe F. What is a nociceptor-specific (class 3) cell? [1]. *Pain*. 1995;62(1):123-127. doi:10.1016/0304-3959(94)00233-5.
148. Mense S. Nociception from skeletal muscle in relation to clinical muscle pain. *Pain*. 1993;54(3):241-289. doi:10.1016/0304-3959(93)90027-M.
149. Willis W, Coggeshall R. *Sensory Mechanisms of the Spinal Cord*. 2nd ed. Plenum Press, New York; 1991.
150. Renn CL, Carozzi VA, Rhee P, Gallop D, Dorsey SG, Cavaletti G. Multimodal assessment of painful peripheral neuropathy induced by chronic oxaliplatin-based chemotherapy in mice. *Mol Pain*. 2011;7:29. doi:10.1186/1744-8069-7-29.
151. Simko LC. *Adults with Congenital Heart Disease: Utilizing Quality of Life and Husted's Nursing Theory as a Conceptual Framework.* Critical care nursing quarterly 22, 1-11 (1999).
152. Holzner B, Bode RK, Hahn EA, et al. Equating EORTC QLQ-C30 and FACT-G scores and its use in oncological research. *Eur J Cancer*. 2006;42:3169-3177. doi:10.1016/j.ejca.2006.08.016.
153. Calhoun E a, Welshman EE, Chang C-H, et al. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *Int J Gynecol Cancer*. 2003;13(6):741-748. http://www.ncbi.nlm.nih.gov/pubmed/14675309. Accessed September 30, 2014.

154. Tofthagen C, Overcash J, Kip K. Falls in persons with chemotherapy-induced peripheral neuropathy. *Support Care Cancer*. 2012;20(3):583-589. doi:10.1007/s00520-011-1127-7.
155. Driessen CML, de Kleine-Bolt KME, Vingerhoets AJJM, Mols F, Vreugdenhil G. Assessing the impact of chemotherapy-induced peripheral neurotoxicity on the quality of life of cancer patients: the introduction of a new measure. *Support Care Cancer*. 2012;20(4):877-881. doi:10.1007/s00520-011-1336-0.
156. Cella DF, Tulsky DS. Quality of life in cancer: definition, purpose, and method of measurement. *Cancer Invest*. 1993;11(3):327-336. doi:10.3109/07357909309024860.
157. Moons P, Van Deyk K, Budts W, De Geest S. Caliber of quality-of-life assessments in congenital heart disease: a plea for more conceptual and methodological rigor. *Arch Pediatr Adolesc Med*. 2004;158(11):1062-1069. doi:10.1001/archpedi.158.11.1062.
158. Carr AJ, Gibson B, Robinson PG. Measuring quality of life: Is quality of life determined by expectations or experience? *BMJ*. 2001;322:1240-1243. doi:10.1136/bmj.322.7296.1240.
159. Hung H-C, Chien T-W, Tsay S-L, Hang H-M, Liang S-Y. Patient and clinical variables account for changes in health- related quality of life and symptom burden as treatment outcomes in colorectal cancer: a longitudinal study. *Asian Pac J Cancer Prev*. 2013;14(3):1905-1909. http://www.ncbi.nlm.nih.gov/pubmed/23679291. Accessed December 1, 2014.
160. Färkkilä N, Sintonen H, Saarto T, et al. Health-related quality of life in colorectal cancer. *Colorectal Dis*. 2013;15(5):e215-22. doi:10.1111/codi.12143.
161. Lewis MA, Zhao F, Jones D, et al. Neuropathic Symptoms and Their Risk Factors in Medical Oncology Outpatients With Colorectal vs. Breast, Lung, or Prostate Cancer: Results From a Prospective Multicenter Study. *J Pain Symptom Manage*. 2015;49(6):1016-1024. doi:10.1016/j.jpainsymman.2014.11.300.
162. Grothey A, Nikcevich DA, Sloan JA, et al. Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7. *J Clin Oncol*. 2011;29(4):421-427. doi:10.1200/JCO.2010.31.5911.
163. Trotti A. The evolution and application of toxicity criteria. *Semin Radiat Oncol*. 2002;12:1-3.
164. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. In: *Seminars in Radiation Oncology*. Vol 13. ; 2003:176-181. doi:10.1016/S1053-4296(03)00031-6.
165. Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: Version 2.0. An improved reference for grading the acute effects of cancer treatment: Impact on radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;47:13-47. doi:10.1016/S0360-3016(99)00559-3.
166. Brundage MD, Pater JL, Zee B. Assessing the Reliability of Two Toxicity Scales: Implications for Interpreting Toxicity Data. *JNCI J Natl Cancer Inst*. 1993;85(14):1138-1148. doi:10.1093/jnci/85.14.1138.
167. Cavaletti G, Cornblath DR, Merkies ISJ, et al. The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to

the first validity and reliability findings. *Ann Oncol*. 2013;24(2):454-462. doi:10.1093/annonc/mds329.
168. Kopec JA, Land SR, Cecchini RS, et al. Validation of a Self-Reported Neurotoxicity Scale in Patients With Operable Colon Cancer Receiving Oxaliplatin. *J Support Oncol*. 2006;4(8):1-8.
169. Backonja M-M, Walk D, Edwards RR, et al. Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. *Clin J Pain*. 2009;25:641-647. doi:10.1097/AJP.0b013e3181a68c7e.
170. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain*. 2006;123(3):231-243. doi:10.1016/j.pain.2006.01.041.
171. Dyck PJ, O'Brien PC, Kosanke JL, Gillen DA, Karnes JL. A 4, 2, and 1 stepping algorithm for quick and accurate estimation of cutaneous sensation threshold. *Neurology*. 1993;43:1508-1512. doi:10.1212/WNL.43.8.1508.
172. Verdugo R, Ochoa JL. Quantitative somatosensory thermotest. A key method for functional evaluation of small calibre afferent channels. *Brain*. 1992;115 (Pt 3:893-913. doi:10.1093/brain/115.3.893.
173. Yarnitsky D, Ochoa JL. Warm and cold specific somatosensory systems. Psychophysical thresholds, reaction times and peripheral conduction velocities. *Brain*. 1991;114 (Pt 4:1819-1826. doi:10.1093/brain/114.4.1819.
174. Cruccu G, Aminoff MJ, Curio G, et al. Recommendations for the clinical use of somatosensory-evoked potentials. *Clin Neurophysiol*. 2008;119(8):1705-1719. doi:10.1016/j.clinph.2008.03.016.
175. Maier C, Baron R, Tölle TR, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain*. 2010;150(3):439-450. doi:10.1016/j.pain.2010.05.002.
176. Tseng CH, Tseng CP, Chong CK. Aging and current perception threshold measured by neurometer in normal Taiwanese adults [1]. *J Am Geriatr Soc*. 2002;50(12):2094-2095. doi:10.1046/j.1532-5415.2002.50627.x.
177. Gröne E, Crispin A, Fleckenstein J, Irnich D, Treede R-D, Lang PM. Test order of quantitative sensory testing facilitates mechanical hyperalgesia in healthy volunteers. *J Pain*. 2012;13(1):73-80. doi:10.1016/j.jpain.2011.10.005.
178. Heldestad V, Linder J, Sellersjö L, Nordh E. Reproducibility and influence of test modality order on thermal perception and thermal pain thresholds in quantitative sensory testing. *Clin Neurophysiol*. 2010;121(11):1878-1885. doi:10.1016/j.clinph.2010.03.055.
179. Sand T, Nilsen KB, Hagen K, Stovner LJ. Repeatability of cold pain and heat pain thresholds: The application of sensory testing in migraine research. *Cephalalgia*. 2010;30(8):904-909. doi:10.1177/0333102409356023.
180. Krumova EK, Geber C, Westermann A, Maier C. Neuropathic pain: Is quantitative sensory testing helpful? *Curr Diab Rep*. 2012;12:393-402. doi:10.1007/s11892-012-0282-7.
181. Wylde V, Palmer S, Learmonth ID, Dieppe P. Test-retest reliability of Quantitative Sensory Testing in knee osteoarthritis and healthy participants. *Osteoarthritis Cartilage*. 2011;19(6):655-658. doi:10.1016/j.joca.2011.02.009.

182. Felix ER, Widerström-Noga EG. Reliability and validity of quantitative sensory testing in persons with spinal cord injury and neuropathic pain. *J Rehabil Res Dev*. 2009;46(1):69-83. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19533521. Accessed September 30, 2014.
183. Moloney NA, Hall TM, Doody CM. Reliability of thermal quantitative sensory testing: a systematic review. *J Rehabil Res Dev*. 2012;49(2):191-207. doi:10.1682/JRRD.2011.03.0044.
184. de Sonnaville JJ, Colly LP, Wijkel D, Heine RJ. The prevalence and determinants of foot ulceration in type II diabetic patients in a primary health care setting. *Diabetes Res Clin Pract*. 1997;35(2-3):149-156. http://www.ncbi.nlm.nih.gov/pubmed/9179471. Accessed September 30, 2014.
185. Tena B, Escobar B, Arguis MJ, Cantero C, Rios J, Gomar C. Reproducibility of Electronic Von Frey and Von Frey monofilaments testing. *Clin J Pain*. 2012;28(4):318-323. doi:10.1097/AJP.0b013e31822f0092.
186. Birke JA, Brandsma JW, Schreuders TA, Piefer A. Sensory testing with monofilaments in Hansen's disease and normal control subjects. *Int J Lepr Other Mycobact Dis*. 2000;68(3):291-298. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11221092. Accessed September 30, 2014.
187. Merkies IS, Schmitz PI, van der Meché FG, van Doorn PA. Reliability and responsiveness of a graduated tuning fork in immune mediated polyneuropathies. The Inflammatory Neuropathy Cause and Treatment (INCAT) Group. *J Neurol Neurosurg Psychiatry*. 2000;68:669-671. doi:10.1136/jnnp.68.5.669.
188. Magerl W, Krumova EK, Baron R, Tölle T, Treede R-D, Maier C. Reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. *Pain*. 2010;151(3):598-605. doi:10.1016/j.pain.2010.07.026.
189. Martina IS, van Koningsveld R, Schmitz PI, van der Meché FG, van Doorn P a. Measuring vibration threshold with a graduated tuning fork in normal aging and in patients with polyneuropathy. European Inflammatory Neuropathy Cause and Treatment (INCAT) group. *J Neurol Neurosurg Psychiatry*. 1998;65:743-747. doi:10.1136/jnnp.65.5.743.
190. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain*. 2006;10(1):77-88. doi:10.1016/j.ejpain.2005.02.003.
191. Claus D, Hilz MJ, Hummer I, Neundörfer B. Methods of measurement of thermal thresholds. *Acta Neurol Scand*. 1987;76(4):288-296. http://www.ncbi.nlm.nih.gov/pubmed/3687380.
192. Dyck PJ, Bushek W, Spring EM, et al. Vibratory and cooling detection thresholds compared with other tests in diagnosing and staging diabetic neuropathy. *Diabetes Care*. 1987;10(4):432-440. doi:10.2337/diacare.10.4.432.
193. Raja S, Meyer R, Ringkamp M, Campbell J. Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R, eds. *Textbook of Pain*. Churchill-Livingstone, Edinburg; 1999:11-57.
194. Couture DJ. Current Perception Threshold Testing (CPT) to Measure Sensory

Fiber Changes After Chemotherapy. 2011.
195. Liu S, Kopacz DJ, Carpenter RL. Quantitative Assessment of Differential Sensory Nerve Block after Lidocaine Spinal Anesthesia. *Anesthesiology*. 1995;82(1):60-63. doi:10.1097/00000542-199501000-00009.
196. Fujihara A, Ukimura O, Iwata T, Miki T. Neuroselective measure of the current perception threshold of A-delta and C-fiber afferents in the lower urinary tract. *Int J Urol*. 2011;18(5):341-349. doi:10.1111/j.1442-2042.2011.02749.x.
197. Tsui BCH, Shakespeare TJ, Leung DH, Tsui JH, Corry GN. Reproducibility of current perception threshold with the Neurometer® vs the Stimpod NMS450 peripheral nerve stimulator in healthy volunteers: an observational study. *Can J Anesth Can d'anesthésie*. 2013;60:753-760. doi:10.1007/s12630-013-9965-z.
198. Gaudreault F, Drolet P, Fallaha M, Varin F. The Reliability of the Current Perception Threshold in Volunteers and Its Applicability in a Clinical Setting. *Anesth Analg*. 2015;120(3):678-683. doi:10.1213/ANE.0000000000000575.
199. Kim HS, Kho HS, Kim YK, Lee SW, Chung SC. Reliability and characteristics of current perception thresholds in the territory of the infraorbital and inferior alveolar nerves. *J Orofac Pain*. 2000;14(4):286-292.
200. Lowenstein L, Jesse K, Kenton K. Comparison of perception threshold testing and thermal-vibratory testing. *Muscle Nerve*. 2008;37(4):514-517. doi:10.1002/mus.20934.
201. Pitei DL, Watkins PJ, Stevens MJ, Edmonds ME. The value of the Neurometer in assessing diabetic neuropathy by measurement of the current perception threshold. *Diabet Med*. 1994;11(9):872-876. doi:10.1111/j.1464-5491.1994.tb00371.x.
202. Katims JJ, Naviasky EH, Rendell MS, Ng LK, Bleecker ML. Constant current sine wave transcutaneous nerve stimulation for the evaluation of peripheral neuropathy. *Arch Phys Med Rehabil*. 1987;68:210-213. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3032128.
203. Takekuma K, Ando F, Niino N, Shimokata H. Age and gender differences in skin sensory threshold assessed by current perception in community-dwelling Japanese. *J Epidemiol*. 2000;10:S33-S38. doi:10.2188/jea.10.1sup_33.
204. Evans ER, Rendell MS, Bartek JP, Bamisedun O, Connor S, Giitter M. Current perception thresholds in ageing. *Age Ageing*. 1992;21:273-279. doi:10.1093/ageing/21.4.273.
205. Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain*. 2011;152(1):14-27. doi:10.1016/j.pain.2010.07.031.
206. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. *Neurology*. 1997;48(2):332-338. doi:10.1212/WNL.48.2.332.
207. Rog DJ, Nurmikko TJ, Friede T, Young C a. Validation and reliability of the Neuropathic Pain Scale (NPS) in multiple sclerosis. *Clin J Pain*. 2007;23(6):473-481. doi:10.1097/AJP.0b013e31805d0c5d.
208. Jensen MP, Friedman M, Bonzo D, Richards P. The Validity of the Neuropathic Pain Scale for Assessing Diabetic Neuropathic Pain in a Clinical Trial. *Clin J Pain*. 2006;22(1):97-103. doi:10.1097/01.ajp.0000173018.64741.62.
209. Jensen MP, Dworkin RH, Gammaitoni AR, Olaleye DO, Oleka N, Galer BS.

Assessment of pain quality in chronic neuropathic and nociceptive pain clinical trials with the Neuropathic Pain Scale. *J Pain*. 2005;6(2):98-106. doi:10.1016/j.jpain.2004.11.002.
210. Dworkin RH, Jensen MP, Gammaitoni AR, Olaleye DO, Galer BS. Symptom Profiles Differ in Patients With Neuropathic Versus Non-neuropathic Pain. *J Pain*. 2007;8(2):118-126. doi:10.1016/j.jpain.2006.06.005.
211. Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. *Clin J Pain*. 2002;18(5):297-301. doi:10.1097/00002508-200209000-00004.
212. Gibbons R, Hedeker D, DuToit S. Advances in analysis of longitudinal data. *Annu Rev Clin Psychol*. 2010;6:79-107. doi:10.1146/annurev.clinpsy.032408.153550.
213. Gelman A, Hill J. *Data Analysis Using Multivariate Regression and Multilevel/hierachical Models*. New York: Cambridge University Press; 2007.
214. Griffith KA, Couture DJ, Zhu S, et al. Evaluation of chemotherapy-induced peripheral neuropathy using current perception threshold and clinical evaluations. *Support Care Cancer*. 2014;22(5):1161-1169. doi:10.1007/s00520-013-2068-0.
215. Treede R, Handwerker HO, Baumgärtner U, Kretzschmar A et. al. Hyperalgesia and allodynia: Taxonomy, assessment adn mechanisms. In: Burne K, Handwerker HO, eds. *Hyperalgesia: Molecular Mechanisms and Clincial Implications*. Seattle, WA: IASP Press, Seattle.; 2004:1-15.
216. Ochoa JL. Quantifying sensation: "Look back in allodynia." In: *European Journal of Pain*. Vol 7. ; 2003:369-374. doi:10.1016/S1090-3801(03)00050-8.
217. Woolf CJ, Mannion RJ. Neuropathic pain: Aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353(9168):1959-1964. doi:10.1016/S0140-6736(99)01307-0.
218. Ziegler EA, Magerl W, Meyer RA, Treede RD. Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. *Brain*. 1999;122(12):2245-2257. doi:10.1093/brain/122.12.2245.
219. Gottrup H, Nielsen J, Arendt-Nielsen L, Jensen TS. The relationship between sensory thresholds and mechanical hyperalgesia in nerve injury. *Pain*. 1998;75(2-3):321-329. doi:10.1016/S0304-3959(98)00011-6.