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The Relationship Between Total Neuropathy Score-reduced, Neuropathy Symptoms and Function.

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by

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ABSTRACT

Chemotherapy Induced Peripheral Neuropathy (CIPN) is a common problem among cancer patients who receive a wide range of chemotherapy. This problem causes a decline in quality of life and increased disabilities. CIPN assessment instruments are either subjective, objective, or a combination of both. So far, there is no agreement on the best way for assessment. The goal of this study was to explore the relationships among subjective and objective CIPN assessment instruments. Specifically, this study aimed to 1) evaluate the relationship between the Total Neuropathy Score-reduced (mainly objective) and patients' function, as measured by the interference scale of the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (subjective); and 2) evaluate the relationship between the Total Neuropathy Score-reduced and neuropathy symptom experience, as measured by the symptom experience scale of the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (Subjective). To achieve those aims, a secondary data analysis for 56 participants who participated in a study entitled: *Group Acupuncture for Treatment of Neuropathy from Chemotherapy* was done. After Pearson correlations were calculated, the study found that there is a positive, weak relationship between the TNSr and the symptom experience scale of the CIPNAT($r=0.34$). A positive, week relationship was found between the TNSr and the interference with activity scale of the CIPNAT($r=0.28$). These results suggest that objective and subjective assessment are not highly correlated, and likely measure different aspects of CIPN. A comprehensive assessment approach is needed for decision making in the clinical oncology setting.

CHAPTER ONE: INTRODUCTION

Chemotherapy Induced Peripheral Neuropathy (CIPN) is a common problem among cancer patients receiving chemotherapy for numerous types of cancers (Grisold, Cavaletti, & Windebank, 2012; Lavoie Smith, Cohen, Pett, & Beck, 2011; Smith, Cohen, Pett, & Beck, 2010). The incidence varies from 10% to 100% depending on the chemotherapy agents used (Balayssac et al., 2011). These chemotherapies include but are not limited to: taxanes, platinums, bortezomib, thalidomide, lenolidamide, and vinca alkaloids (Argyriou, Cavaletti, Bruna, Kyritsis, & Kalofonos, 2014; Chaudhry, Cornblath, Polydefkis, Ferguson, & Borrello, 2008; Paice, 2009; Visovsky, 2003; Wolf et al., 2012).

CIPN leads to sensory, motor, and autonomic deficits (Dermitzakis et al., 2016). Most of the symptoms are sensory and present with stocking and glove distribution causing numbness, tingling, discomfort and neuropathic pain (Cavaletti, Alberti, & Marmiroli, 2015; Dougherty, Cata, Burton, Vu, & Weng, 2007; Jaggi & Singh, 2012; Koeppen et al., 2004; Tofthagen, McAllister, & Visovsky, 2013). These symptoms start distally in the hands and feet moving proximally with cumulative chemotherapy doses (Dougherty, Cata, Cordella, Burton, & Weng, 2004). Such symptoms, by their nature, are subjective and thus must be reported by the patient.

Combined sensory, motor, and autonomic neuropathies negatively affect patients' quality of life, functional ability, sleep, and balance (Bakitas, 2007; Beijers, Mols, & Vreugdenhil, 2014; Beijers, Mols, Dercksen, Driessen, & Vreugdenhil, 2014; Binda et al., 2013; Calhoun et al., 2003; Driessen, de Kleine-Bolt, Vingerhoets, Mols, & Vreugdenhil, 2012; Hong,

Tian, & Wu, 2014; Kneis et al., 2015; Lane, 2005; Oerlemans et al., 2014; Park, Lin, & Kiernan, 2012b; Smith, Beck, & Cohen, 2008). These devastating effects may lead clinicians to change the chemotherapy regimen or reduce the dose (Cavaletti et al., 2003; Kim, Dougherty, & Abdi, 2015). Some of these problems, such as balance, can be assessed objectively by the clinicians.

Chemotherapy induced peripheral neuropathy assessment instruments are either objective, subjective, or a combination of both. Objective instruments can use physical exam, sensory quantification such as using monofilaments and vibration sensation, direct nerve testing such as using skin biopsies, nerve ultrasound, nerve conduction studies (NCS), and nerve excitability assessment (NEA). Because of their complexities, insurance coverage, and provider comfort level, these instruments also are rarely used in the oncology clinical setting (Cornblath et al., 1999).

Most CIPN assessment instruments are subjective and depend on patient reporting. Examples of these instruments are the Patient Neurotoxicity Questionnaire (Kuroi et al., 2008; Shimozuma et al., 2009), the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (Tofthagen, McMillan, & Kip, 2011), The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity scale (Calhoun et al., 2003; Griffith et al., 2014; Yoo & Cho, 2014), the Chemotherapy Induced Neurotoxicity Questionnaire (CINQ) (Leonard et al., 2005), The Treatment-Induced Neuropathy Assessment Scale (TNAS) (Mendoza et al., 2015), the European Organization for Research and Treatment of Cancer EROTC-QOL-CIPN-20 (Cull et al., 2001; Lavoie Smith et al., 2013; Padman et al., 2015), the Peripheral Neuropathy Scale (Cavaletti et al., 2003; Cavaletti et al., 2007), and the Rasch-built Disability Scale for patients with CIPN (Binda et al., 2013).

These subjective instruments are important in understanding the symptoms and effects of CIPN on quality of life (QOL). Due to time constraints, unfamiliarity, and discrepancy between the provider and patient perception, these subjective instruments are rarely used in the clinical oncology setting either (Basch et al., 2012; Smith et al., 2014; Visovsky et al., 2012).

Due to the assessment deficiencies of both the objective and the subjective instruments, using a combined objective/subjective instruments such as the Total Neuropathy Scores (TNS) and its various versions, may be a more feasible approach in the clinical setting, if they correspond well with patient symptoms. This instrument was initially reported for use in neuropathy in 1994 (Cavaletti et al., 2003). It underwent multiple studies and modifications to improve its reliability and validity (Binda, Cavaletti, Cornblath, Merkies, & group, 2015; Cavaletti et al., 2003; Lavoie Smith et al., 2011).

Statement of the Problem

CIPN is a grave problem affecting the quality of life for many cancer patients; thus, CIPN needs early detection to prevent long term damage. However, there is disagreement among clinicians on the best method for assessment in the clinical oncology setting (Izycki et al., 2016). Furthermore, the relationship between patients reported CIPN symptoms and clinical assessments such as the TNSr have not been adequately explored. Neurologists may depend mainly on objective measures such as nerve conduction studies and neurological examination and may overlook patients' input. On the other hand, nursing researchers have relied more on subjective measures and patient reported outcomes, while oncologists have relied on the National Cancer Institute-Common Terminology Criteria (NCI-CTCAE) (Cavaletti et al., 2007).This disagreement on the best way to assess CIPN may make it hard to understand the problem of

CIPN in the clinical setting. Oncology practices need a unified approach to assessment of CIPN, so that clearer communication is possible among providers (Tanay, Armes, & Ream, 2016).

The purpose of this study is to evaluate relationships among the Total Neuropathy Score-reduced, neuropathy symptoms, and function. If this instrument has a strong relationship with neuropathy symptoms and function, it can be used to help guide clinicians in treatment strategies such as chemotherapy treatment choice, dose reduction, or discontinuation of the neurotoxic chemotherapy thus preventing irreversible side effects and functional disabilities from CIPN. Also, it may assist providers in communicating with each other about patients. This study aims to evaluate the validity of the TNSr in assessment of neuropathy symptoms and function.

Specific Aims

The specific aims of this study were as follows:

Aim 1: To evaluate the relationship between the Total Neuropathy Score-reduced and patients' function, as measured by the interference scale of the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool.

Aim 2: To evaluate the relationship between the Total Neuropathy Score-reduced and neuropathy symptom experience, as measured by the symptom experience scale of the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool.

Significance to Nursing

CIPN is a common problem among patients treated for cancer (Grisold et al., 2012). However, there is no widespread agreement on how to assess this pervasive problem (Izycki et al., 2016). If a strong relationship is found between the TNSr, neuropathy symptoms, and patient function it may have supported the validity of the TNSr for use with patients with CIPN. Such a valid instrument would be very beneficial to oncology nurse practitioner and oncology clinicians.

The TNSr is a short tool (using five items only). It addresses both the subjective patient input (symptom extension into the extremities), and addresses the objective clinician input (pin sensibility, vibration sensibility, muscle strength, and deep tendon reflexes). Studying this relationship contributes evidence of construct validity for this instrument as it connects the TNSr with some CIPN outcomes. Finding a strong relationship between TNSr, neuropathy symptoms, and patient function may lead to consistent and meaningful CIPN assessment. It may also help in early CIPN detection, leading to fewer complications, falls, and balance issues. It also may help researchers in evaluating new CIPN treatment modalities.

CHAPTER TWO: REVIEW OF THE LITERATURE

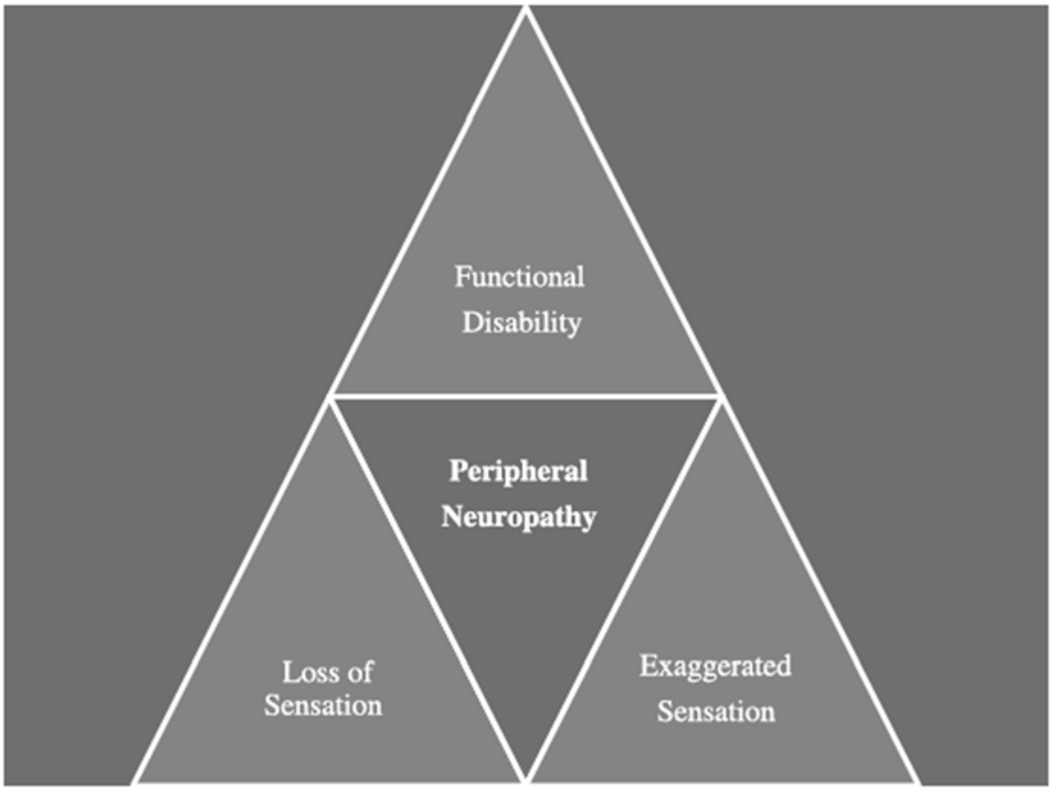
This chapter reviews and summarizes the current literature on Chemotherapy Induced Peripheral Neuropathy (CIPN) assessment instruments. A literature search was conducted using the following search terms: chemotherapy induced peripheral neuropathy assessment, neuropathy, and polyneuropathy. The search was conducted using PUBMED. All articles that met inclusion criteria (indexed in PUBMED, written in the English language, used with human subjects, evaluating CIPN instrument reliability and validity, published between 2011 and 2017) were included. Literature review before 2011 is available in two comprehensive reviews (Griffith, Merkies, Hill, & Cornblath, 2010; Shimozuma et al., 2009). This chapter includes the conceptual framework, CIPN screening, objective CIPN instruments, subjective CIPN instruments, history of the Total Neuropathy Score in CIPN assessment, and CIPN assessment of patient function.

Conceptual Framework

Neuropathy, neurotoxicity, polyneuropathy, neuropathic pain in the presence of chemotherapy, and painful neuropathy are used in the literature as attributes of CIPN (Fallon et al., 2015; Gewandter et al., 2015; Koeppen, 2014; Kroigard et al., 2014; Wickham, 2007). CIPN can be conceptualized as having three major components: loss of sensation, exaggerated sensation, and functional disabilities (Tofthagen, Kip, Passmore, Loy, & Berry, 2016) (Figure 1). The loss of sensation can be clinically evaluated by pinprick, vibration, light touch, and joint

position sensations(Alberti et al., 2014), while exaggerated sensations include tingling, electric-like sensations, and neuropathic pain, which are primarily evaluated by patient report (Lavoie Smith et al., 2011; Tofthagen, 2010). Functional disabilities include but are not limited to driving, writing, picking things up, work, sleep, walking, hobbies, household duties, walking, cooking, and exercise (Binda et al., 2013; Tofthagen, 2010).

Figure 1. Chemotherapy Induced Peripheral Neuropathy Conceptual Framework.



Source: (Tofthagen et al., 2016). Used with permission.

CIPN Screening Instruments

CIPN screening is needed before and during chemotherapy treatment (Simon, Danso, Alberico, Basch, & Bennett, 2017). This will help in early detection, CIPN treatment, and help in CIPN research.

The National Cancer Institute-Common Toxicity Criteria (NCI-CTC) is a widely used neuropathy screening instrument (Basch et al., 2014; Chu, Lee, Lee, & Cleeland, 2015; Visovsky et al., 2012). It includes sensory and motor sections. This instrument is rated by the provider and ranges from 0 (Normal) to 4 (permanent sensory loss) in the sensory section or (paralysis) in the motor section (Kautio et al., 2011). This instrument has the advantage of being short and quick which made it the recommended instrument for clinical trials by the Food and Drug Administration (FDA) and the NCI. This instrument went through multiple modifications and name changes through the years to be called the Common Terminology Criteria for Adverse Events (CTCAE) and NCI-CTCAE (Miyoshi et al., 2015). Despite its easy usage, it lacks flexibility in score variance and lacks both patient input and clinical neurologic examination (Basch et al., 2014; Cavaletti et al., 2015).

The reliability and the validity of the NCI-CTCAE were tested extensively. The kappa reliability coefficient was reported to be 0.98 (Miyoshi et al., 2015). Validity was evidenced as patients had higher scores with cumulative chemotherapy dosing (Pereira et al., 2016; Velasco et al., 2014). Further evidence of validity was reported by correlating it to the Total Neuropathy Score (TNS) and its different versions. Most of the studies reported moderate to high correlation with the sensory section (0.4 to 0.6) and low correlation with the motor section (0.25) (Alberti et al., 2014; Frigeni et al., 2011; Lavoie Smith et al., 2013; Lavoie Smith et al., 2011; Park et al.,

2011). Despite the good validity scores of the sensory section of the NCI-CTCAE, it fails to predict CIPN compared to other instruments such as the Patient Neurotoxicity Questionnaire (PNQ) (Shimozuma et al., 2012).

To fill the gap of deficient patient reported CIPN screening instruments, the National Cancer Institute developed a new patient reported instrument called PRO-CTCAE (Dueck et al., 2015; Hay et al., 2014). The internal consistency was high with an intra-class correlation coefficient of 0.76; the validity was found to be satisfactory when correlating it with a health related quality of life measure (r= 0.34) (Dueck et al., 2015). This standardized approach to CIPN screening has been widely adapted in clinical settings, but is of little use in understanding the specific symptoms a patient may be having, or how CIPN is affecting their daily life.

CIPN Assessment

After the screening process for CIPN is complete, a more comprehensive approach is needed. This approach includes medical history, symptom review, and physical exam. Further assessment includes the use of CIPN objective assessment instruments and/or subjective instruments. Some of the instruments use combined subjective/objective measures such as the TNSr.

A comprehensive neurologic clinical assessment is the first step in understanding the status of CIPN. It consists of subjective questions followed by a thorough physical exam. The subjective part consists of relevant questions appropriate for patient medical history. Some of these questions address history of stroke, memory ability, gait, falls, and senses of vision and hearing (Corey-Bloom & David, 2009).

The second step in the objective neurologic evaluation is to check the gait, muscle strength, manual dexterity, vibration sensation, and deep tendon reflexes. Vision, hearing, and memory are added in the elderly patients (Corey-Bloom & David, 2009). Gait testing includes having patients rise from a chair without using their arms, walk on tiptoes, heels, and tandem for 10-20 feet. Normally the gait is smooth, rhythmic, and effortless. The hand opposite arm swing is coordinated, and turns are smooth (Jarvis & Jarvis, 2004).

Muscle strength can be done on upper or lower extremities. It is rated from 5 to 0. The rating is as follows: 5(Movement against full resistance of examiner), 4(Movement against some resistance), 3(Movement against gravity, not resistance), 2(Movement only with gravity eliminated), 1(A flicker or trace of voluntary movement), 0(No voluntary movement).

Deep tendon reflexes are assessed to check the homeostasis between the nerves, the cerebral cortex, and the spinal cord. The most commonly used scales to assess deep tendon reflexes are the Mayo Clinic Reflex Scale (rated from -4 to +4) and the National Institute of Neurological Disorders and Stroke scale (NIND) (rated 0: absent to 4: reflex enhanced more than normal or clonus). The NIND inter-observer reliability was assessed using Kappa coefficient and was up to 0.89 (Litvan et al., 1996). In 1990, 28% of the providers using the Mayo Clinic Reflex disagreed on the rating by two or more points (Stam & van Crevel, 1990). In another study, the highest inter-observer reliability Kappa was found to be 0.29 (Manschot, van Passel, Buskens, Algra, & van Gijn, 1998). Given the doubts regarding the reliability of conventional deep tendon reflexes scales, a new measure was developed that involved testing the use of electromyographic deep tendon reflexes. This measure uses a conventional reflex hammer connected by a wire to a myography machine. In 2009 study, this instrument detected neuropathy in 60% of patients that the conventional method failed in this detection (Sharma, Saadia, Facca, Resnick, & Ayyar,

2009). Once the initial physical exam is done, the provider may choose to move to other objective assessment measures instruments.

Objective CIPN Assessment

Objective assessment includes measures of sensory quantification and use touch sensation, bump detection, pressure sensation. It also includes direct testing of nerves either by biopsy, ultrasound or nerve conduction studies.

Sensory Quantification. Touch sensation testing can either be done by Semmes-Weinstein (von Frey) monofilament, pumps detection device, weighted needle device, or Pressure-Specified Sensory Device. The Semmes-Weinstein monofilaments have different weights and are usually presented in a kit. The monofilament weight can range from 0.02 grams to 300 grams (Kosturakis et al., 2014; Ruhdorfer et al., 2015; Ward et al., 2014).The normal sensory threshold is 0.05 gram on the hands (da Silva Simao, Teixeira, Souza, & de Paula Lima, 2014) and 6 gram on the feet (Thomson, Potter, Finch, & Paisey, 2008).

The bumps detection device has glass plates with variant elevated bumps on them. The patient uses his/her index finger of their dominant hand to identify the smallest bump. The detection threshold is determined to be the smallest bump correctly identified in sequence to the next two higher bumps. In a comparison between healthy individuals and patients receiving chemo, plates containing pumps with a diameter of 550 millimeters (mm) and height ranges from 2.5-26 mm. In a study, the mean bump detection threshold for CIPN patients was 6.30mm but only 3.3mm for volunteers ($P<.01$) (Kosturakis et al., 2014).

Pressure sensation can be tested by using either the weighted needle device or Pressure-Specified Sensory Device. The weighted needle device weights range from 8 to 128 g. While

pressure is applied for one second in ascending order, patients are instructed to state whether the sensation produced by each stimulus is that of touch, pressure, sharpness, or pain. The sharpness detection threshold is defined as the mean force deemed sharp or painful (Kosturakis et al., 2014). The Pressure-Specified Sensory Device has two rounded prongs, the pressure is applied to the skin by both prongs, and the patient presses a red button connected to the machine indicating the feeling of pressure difference between the two prongs (Ruhdorfer et al., 2015).

In a study reported in 2016, some quantitative sensory measures (cold detection, heat detection, and cutaneous detection) were tested on a cohort of 30 patients correlated with the NCI-CTCVE. No reliability data was found, but validity was tested by Pearson correlation coefficient. Moderate correlations between cold detection threshold r =.50, heat detection threshold r=0.39, and cutaneous detection threshold r=0.42 were described (Reddy et al., 2016).

Direct Nerve Testing. Direct nerve testing can be done by confocal microscopy of the skin or cornea, skin ultrasound, skin biopsy, nerve biopsy, or nerve excitability. Confocal microscopy is a newer laser imaging technique for visualizing changes in skin structure that can identify CIPN. This technique was used in a cohort of multiple myeloma patients and compared to sensory and motor perception using skin temperature, grooved pegboard test, monofilaments, and bumps detection test. Significant differences were found when comparing healthy individuals to individuals who received chemotherapy, which supports validity (Kosturakis et al., 2014). In another study, similar results were obtained when corneal nerve microscopy was correlated with the cumulative dose of chemotherapy with a resulting strong, negative correlation (-0.8) (Ferdousi et al., 2015).

A skin biopsy can be done to test for small fiber and intraepidermal nerve fiber density. This method can be approved by insurance in cases of unidentified neuropathy etiology and has been tested against other neuropathy assessment methods and shown to be a good quantitative measure. Direct nerve visualization can be done by direct ultrasound using a laser Doppler imager (Sharma, Venkitaraman, Vas, & Rayman, 2015).

Small fiber neuropathy can also be tested using the Sudoscan (a 3-min test), which is a machine used to measures the Electrochemical Skin Conductance (ESC) measured in milliseconds (ms). This is a non-invasive instrument applied to either the hands or the feet. In one study, a comparison was done between Sudoscan and the Total Neuropathy Score-Clinical (TNSc) (7 item instrument) on patients who received oxaliplatin, paclitaxel, other drugs, or both drugs. For patients receiving oxaliplatin, the mean hands ESC changed from 73ms to 63ms, feet ESC from 77ms to 66ms, while TNSc mean changed from 2.9 to 4.3. For patients receiving paclitaxel, values of both hands and feet with a corresponding TNSc of <2, the ESC changed from 70ms to 73ms. For TNSc of ≥ 6, the ESC changed from 59ms to 64ms, demonstrating the validity of the Sudoscan. In this study, there was no reliability data reported (Saad et al., 2016).

Nerve Electrophysiological Studies. Nerve electrophysiological studies include nerve amplitude, electromyography, nerve conduction velocity, and nerve excitability studies (Park, Lin, & Kiernan, 2012a). In nerve amplitude, the change of nerve electrical current is measured by special equipment. Decreased nerve amplitude can indicate a decrease in nerve conduction and thus some form of neuropathy. The electromyography uses a similar approach but testing both nerve and muscle function.

Similarly, nerve conduction velocity (speed) and nerve excitability (reaction to nerve stimulator) can be used. A decline in either, suggests a demyelinating neuropathy indicting neuronal harm as seen in CIPN (Kaley & Deangelis, 2009). The usual sites for measuring nerve conduction in CIPN are the peroneal, tibial, sural, median, and superficial radial nerves (Park et al., 2013). In a study using nerve excitability, it was found that there is a 90-100 millisecond excitability difference between patients who received chemotherapy and patients who did not. This is good evidence for instrument validity (Park et al., 2012a).

Despite the objectivity of these studies, they still lack patient input and do not address patients' experience. It is crucial that we find an assessment instrument that is comprehensive, objective, and adequately reflects CIPN symptoms.

Subjective CIPN Assessment

Subjective assessment instruments use patient questionnaires and may address one or more of the following issues: neuropathy symptoms, quality of life (QOL), patient functioning, or interference with life. Examples of these instruments are the Patient Neurotoxicity Questionnaire (Kuroi et al., 2008; Shimozuma et al., 2009), the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (Tofthagen et al., 2011) , The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity scale (Calhoun et al., 2003; Griffith et al., 2014; Yoo & Cho, 2014), the Chemotherapy Induced Neurotoxicity Questionnaire (CINQ) (Leonard et al., 2005), The Treatment-Induced Neuropathy Assessment Scale (TNAS) (Mendoza et al., 2015), the European Organization for Research and Treatment and Cancer EROTC-QOL-CIPN-20 (Cull et al., 2001; Lavoie Smith et al., 2013; Padman et al., 2015), the

Peripheral Neuropathy Scale (Cavaletti et al., 2003; Cavaletti et al., 2007), and the Rasch-built Disability Scale for patients with CIPN (Binda et al., 2013).

These subjective instruments are important in understanding the symptoms and effects of CIPN on QOL. Due to time constrains, unfamiliarity, and discrepancy between the provider & patient perception, these instruments are rarely used in the clinical oncology setting (Basch et al., 2012; Smith et al., 2014; Visovsky et al., 2012).

The Patient Neurotoxicity Questionnaire (PNQ). The PNQ has two items graded from A to E, with A representing no symptoms and E representing worst symptoms. One item is sensory and asks about numbness, pain, or tingling. The second item is motor and asks about weakness. A feasibility study was done that shows the usefulness of this instrument in making treatment decisions (Kuroi et al., 2008). In one study, the sensory item correlated moderately with sensory NCI-CTC (r=0.58), FACT-Taxane (r=0.51), while the motor item correlated with FACT- Taxane (r=0.57) (Kuroi et al., 2009). In another study, the correlation of the sensory item with NCI-CTC was higher than the motor item (r=0.79) (Bennett et al., 2012). This moderate to high correlation supports validity for using it to assess CIPN with the limitation of only two patient reported items.

Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT). In 2011, a new instrument was developed, called the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT). It was developed based on the theory of Unpleasant Symptoms that suggests that complete assessment of unpleasant symptoms should include evaluation of symptom occurrence, severity, distress, frequency, and interference with daily activities. The CIPNAT has two assessment scales. The first is the symptom experience scale comprising nine

neuropathy symptoms with their characteristics (occurrence, severity, distress, and frequency). Each symptom is answered with yes/no question, and symptom severity, distress, and frequency are answered on a 0-10 scale. Total possible score from each symptom is 31. Total for all items is 279. The interference with life scale is comprised of 14 items including walking, picking up objects, holding into objects, driving, working, participating in hobbies or leisure activities, exercising, sexual activity, sleeping, relationships, writing, usual household chores, and enjoyment of life. Each item is scored from 0-10 with a total possible score of 140. Content validity index was acceptable at 0.95. Discriminant validity data were provided by correlation with the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity scale (FACT/GOG-Ntx) (r = 0.83). High test-retest correlations (r = 0.92, P .001), Cronbach's alpha = .95, and significant item-to-total correlations ranging from 0.38 to 0.70 provided evidence of reliability (Tofthagen, McMillan, & Kip, 2011). In a study assessing the effect of CIPN, the CIPNAT was found to be a good predictor of hospital anxiety, depression, and functional status (Kim, Lee, Kim, & Oh, 2015).

The Chemotherapy Induced Neurotoxicity Questionnaire (CINQ). The CINQ consists of three sections. Those sections are upper extremity symptoms, lower extremity symptoms, and oral/ facial symptoms. The first section asks about the presence of tingling (pins and needles), numbness, difficulty telling the difference between rough and smooth surfaces, difficulty feeling hot things, difficulty feeling cold things, a greater than normal sense of touch (i.e. putting on gloves), a greater than normal sense of touch (i.e. putting on gloves), burning pain or discomfort without cold, burning pain or discomfort with cold, difficulty identifying objects in your hand (i.e. coin), and involuntary hand movements. The second section asks about tingling (pins and needles), difficulty telling the difference between rough and smooth surfaces, difficulty

feeling hot things, difficulty feeling cold things, a greater than normal sense of touch (i.e. discomfort with socks), burning pain or discomfort without cold, burning pain or discomfort with cold, and legs feel heavy. The third section asks about the presence of jaw pain, eyelid drooping, throat discomfort, ear pain, tingling in mouth, difficulty with speech, eye burning or discomfort, loss of any vision, feeling shock/pain down back, problems with breathing (Leonard et al., 2005).

These questions in these three sections are answered by yes/no. If yes then it asks two questions regarding effects on QOL and effects on daily activities. The first is how much of the symptoms did you have? Rated from 1 to 5 (Hardly any → Very much, and did the symptoms affect your daily activities? Rated from 1to 5 (Hardly at all bothered → extremely bothered). The validity of this instrument was evident by the increased symptoms with subsequent chemotherapy cycles. No reliability data was reported (Leonard et al., 2005). In another study, this instrument was modified and tested against the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group/Neurotoxicity (FACT/GOG-Ntx) questionnaire. It was valid and strongly correlated with (FACT/GOG-Ntx) questionnaire (r=-.7). No reliability data was reported (Driessen et al., 2012).

The Treatment-Induced Neuropathy Assessment Scale (TNAS). The TNAS was published in 2015 reporting data collected from 248 patients between 2008 and 2013. The instrument consists of 13 items based on other instruments and expert input. The 13 items were; numbness/tingling in hands/feet at its worst, cramps in hands/feet at their worst, sensations of pins/needles in arms/legs at their worst, trouble walking because of loss of feeling in legs/feet at its worst, feelings of coldness in hands/feet/fingers at its worst, difficulty with balance because of loss of feeling in legs/feet at its worst, trouble grasping small objects (e.g., buttoning buttons, handling coins, holding a pen)at its worst, hot/burning sensations in hands/feet at their worst,

swelling in hands/feet at its worst, sensations of electric shock at their worst, discomfort when touching things at its worst, discomfort when skin comes into contact with something (e.g., blanket, clothing) at its worst, and pain when touching cold things at its worst. The 13 items were divided into two subscales a sensory and a motor. Reliability was found to be high with Cronbach's alpha >0.8. Validity was evaluated by correlating it to EROTC-QLQ-CIPN20. Correlation with the sensory section was 0.64, and with the motor section was 0.7 (Mendoza et al., 2015).

Despite the availability of multiple CIPN subjective assessment tool, new measures are being developed and tested. This stresses both the need for a good instrument and the lack of consensus among the researchers and clinicians on the best approach.

The History of the Total Neuropathy Score in CIPN Assessment

A combination of both subjective and objective assessment measures may give a more comprehensive view of CIPN. These methods combine objective assessment with the patient subjective assessment which is important to the individual patient experience. The first used CIPN assessment instrument that uses combined approaches is the Total Neuropathy Score (TNS) (Cornblath et al., 1999).

The Total Neuropathy Score, published in 1994, was tested and validated to evaluate CIPN. It includes patients' reporting of motor and sensory symptoms, pin sensibility, vibration examination, deep tendon reflexes, and nerve conduction studies. The TNS demonstrated good inter-rater reliability (0.94) and intra-rater reliability (0.97) (Chaudhry, Rowinsky, Sartorius, Donehower, & Cornblath, 1994). In 2003, a modified version of the TNS was developed by omitting the nerve conduction studies; it was called the Total Neuropathy Score-reduced (TNSr).

The study demonstrated a strong correlation between TNS and TNSr (r=.97). Scores for all items of the TNSr and TNS items increased in the study sample after receiving chemotherapy and with cumulative dose (Cavaletti et al., 2003). Validity data also was provided in 2006 by comparing the TNS to four other measures; The Modified Total Neuropathy Score (mTNS), the Michigan Diabetes Neuropathy scores (MDNS), quantitative touch thresholds, and quantitative vibration thresholds. A strong correlation was found between the TNS and the mTNS (r=0.99) and a slightly weaker correlation between the mTNS and the MDNS (r=0.71). However, this study did not report reliability scores (Wampler, Miaskowski, Byl, Rugo, & Topp, 2006).

A similar approach was done to test a seven item revised version (Total Neuropathy Scale clinical (TNSc) in 2010 and 2013. The TNSc items are sensory, motor, autonomic, pin-prick, vibration, strength, and deep tendon reflexes. This instrument was subject to multiple methods of testing to insure its fit to be used in the clinical setting and its ability to predict patient function. Reliability was evidenced by a Cronbach's alpha of 0.8, and validity was evidenced by correlating it to the modified Inflammatory Neuropathy Cause and Treatment (INCAT) group sensory sum score (mISS) with a Spearman factor of r=0.7 (Argyriou et al., 2013; Cavaletti et al., 2013; Cavaletti et al., 2010).

In a different line of research, other versions of the TNS were tested. The Total Neuropathy Score-reduced (TNSr) consisting of five items and the Total Neuropathy Score-reduced-short form (TNSr-SF) consisting of three items. The five items are sensory symptoms (the worst proximal extension of tingling, numbness, neuropathic pain), vibration sense, pin sensibility, motor strength, and tendon reflexes. The TNSr-SF has the same items excluding the motor strength, pin sensibility, and deep tendon reflexes. The TNSr-SF has a neuropathic pain item added. These two instruments show good validity to be used in the clinical field. The

validity of TNSr was tested by correlating it with the Neuropathy Pain Scale (NPS-CIN) (r= 0.51) and the sensory NCI-CTC scores (r=0.63) (Lavoie Smith et al., 2011; Smith et al., 2008). Inter-rater reliability of the TNSc (a similar measure to TNSr) was found to be 0.8 (Cavaletti et al., 2013).

In a later study, the TNSc was transformed using the Rasch statistical technique to study the factors affecting the use of TNSc in clinical practice. It was found that the seven item instrument did not fit the Rasch statistical model but when autonomic symptoms and deep tendon reflexes (DTR) were removed, the fit improved. Thus it was recommended to remove those 2 items from the instrument and it was called Rasch-Transformed Total Neuropathy Score clinical version (RT-TNSc) (Binda et al., 2015).

In summary of the literature pertaining to the TNS and its different version, the TNSc is valid and reliable with Cronbach's alpha score up to 0.8 and Spearman correlation up to 0.7 (Alberti et al., 2014; Binda et al., 2013; Briani et al., 2014; Griffith et al., 2014; Velasco et al., 2014). The validity of the TNS-SF is documented, but the validity needs further testing. The TNSc is an increasingly used instrument which combines both subjective and objective measures making it one of the instruments that can be used in the clinical oncology setting (Cavaletti et al., 2015).

There are multiple ways to assess CIPN, and concentrated efforts to develop a standard assessment instrument have been a focus of research (Binda et al., 2015; Lavoie Smith et al., 2013; Tofthagen et al., 2011). These include innovative approaches that use subjective instruments, objective instruments, or combined (subjective and objective) instruments. On one hand, the objective instruments may be hard to use by most health care providers because of the

special skills and sophisticated equipment that these instruments require. This is apparent in instruments using nerve conduction studies, skin biopsies, ophthalmic testing, or ultrasound (Briani et al., 2013; Burakgazi et al., 2011; Ferdousi et al., 2015; Park et al., 2012b). On the other hand, subjective instruments are time consuming, which may discourage consistent use in the clinical setting (Shimozuma et al., 2009). The only assessment instruments that have combined objective and subjective assessment methods are the TNS and its different versions. (Alberti et al., 2014; Binda et al., 2015; Briani et al., 2014; Burakgazi et al., 2011; Frigeni et al., 2011; Lavoie Smith et al., 2013; Lavoie Smith et al., 2011; Shimozuma et al., 2009; Smith et al., 2008; Velasco et al., 2014). The components of various versions of the TNS are outlined in Table 1.

Table 1. Total Neuropathy Score (TNS) and its versions used in assessing adults.

	Sensory Symptoms	Motor Symptoms	Autonomic Symptoms	Pin-Prick	Muscle Strength	DTR	Vibration Sense	Sural NCS[1]	Peroneal NCS[1]
TNS	X	X	X	X	X	X	X	X	X
TNSc	X	X	X	X	X	X	X		
RT-TNSc	X	X		X	X		X		
TNSr	X			X	X	X	X		
mTNS	X	X	X	X	X	X	X		
TNSr-SF	X						X		

[1.]NCS: Nerve Conduction Studies.

CIPN Assessment and Patient Function

The assessment of CIPN has been tied to patient function (Binda et al., 2013; Wolf et al., 2012). Some assessment instruments use function as an integrated part of the assessment instrument. Other instruments used that as the effect or the consequence of CIPN. One of these instruments is the EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy (EROTC-QLQ-CIPN20). This instrument has three subscales sensory, motor, and autonomic. The motor has items addressing writing, and manipulating small objects as patients' function items. The reliability and validity were tested in a 2005 study reporting a

Cronbach's alpha coefficient of 0.82, 0.73 and 0.76 for the sensory, motor and autonomic scales. Validity was studied by using expert and patient input, but no statistical results reported (Postma et al., 2005).

Other assessment instruments looked at the patients' function as a consequence of the CIPN. An example is the interference with activity scale of the CIPNAT. It includes items such as walking, picking up objects, holding into objects, driving, working, participating in hobbies or leisure activities, exercising, sexual activity, sleeping, relationships, writing, usual household chores (Tofthagen et al., 2011).

CHAPTER THREE: METHODS

This chapter describes the study methods: The design, setting and sample, and measures used in the study. It also describes the study procedure, and data management and analysis.

Design

This is a cross sectional study designed to test the relationship among Total Neuropathy Score-reduced, neuropathy symptoms, and function. This instrument is a short composite of subjective and objective measures of CIPN. To achieve this goal, a secondary data analysis was conducted using data collected from a study entitled *Group Acupuncture for Treatment of Neuropathy from Chemotherapy* (PI: Tofthagen).

Setting and Sample

The parent study was conducted at Florida Cancer Specialists facility in Largo, Florida. A total of 56 patients were included. Inclusion criteria included that patients had to have a cancer diagnosis; had received at least one prior treatment with neurotoxic chemotherapy (any taxane, platinum based chemotherapeutic agent, vinca-alkaloid, thalidomide, or bortezomib) within the past 10 years; not be currently receiving neurotoxic chemotherapy ; be able to speak, read, and write in English; have numbness/tingling/or discomfort in the hands or feet with a minimum severity score of three on a 0-10 scale; and have written clearance from their oncologist to receive acupuncture. Patients were excluded from the study if they are already receiving acupuncture for any reason or if they were pregnant or breastfeeding.

Measures

The Total Neuropathy Score-reduced

The TNSr includes one subjective item (the worst proximal extension of tingling, numbness, neuropathic pain), and four objective items: (pin sensibility, vibration sensibility, muscle strength, and tendon reflexes). The tingling symptom extension is scaled from 0 (none) to 4 (extension above the knee or elbow). To test pin sensibility, a safety pin is used and is scaled from 0 (normal) to 4 (reduced above knee or elbow). To test vibration sensibility, a vibrating 128 Hz tuning fork is used and is scaled from 0 (normal) to 4 (reduced above knee or elbow). Muscle strength scaled from 0 (normal) to 4 (paralysis), and deep tendon reflexes scaled from 0 (normal) to 4 (all reflexes absent). The total scores of the TNSr range from 0 to 20. The TNSr has demonstrated good reliability and validity. The inter-rater reliability was tested resulting in no significant difference between two raters ($z= -1.13$, $P<.26$). The validity of the TNSr was tested by correlating it with the Neuropathy Pain Scale (NPS-CIN) ($r=.69$) (Smith et al., 2010).

The Chemotherapy Induced Peripheral Neuropathy Assessment Tool

The CIPNAT has two assessment scales. One is the symptom assessment scale, and the other is the interference with activity scale. Validity and reliability of the total CIPNAT were tested by administering it to two groups of patients. One group had neuropathy, and the other did not. Content validity index generated by a panel of experts was acceptable at 0.95. Convergent validity data were provided by correlation with the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity Scale (FACT/GOG-Ntx) ($r = 0.83$, $P < .001$) and differences between the compared groups ($t = 7.66$, $P < .001$) provided evidence of discriminant validity. High test-retest correlations ($r = 0.92$, $P < .001$), Cronbach's alpha = .95,

and significant item-to-total correlations ranging from 0.38 to 0.70 provided evidence of reliability (Tofthagen et al., 2011).

The Symptom Assessment Scale. The symptom experience scale has nine neuropathy symptoms with their characteristics (occurrence, severity, distress, and frequency). The patients indicate whether each symptom is present by answering a yes/no question and if yes, the symptom description items are answered on 0-10 scales. The total possible score from each symptom is 31. The total score for all items is 279.

Discriminant validity of the symptom experience scale was tested by comparing two groups of patients (one group had neuropathy and the other group did not) ($t = 8.81$, $P < .001$). A strong evidence of reliability was found by correlating a test-retest results ($r = 0.89$, $P < .001$). Internal consistency Cronbach's alpha coefficients were high for the symptom experience items (alpha = .93).

The Interference with Activity Scale. The interference with activity scale has 14 items including walking, picking up objects, holding into objects, driving, working, participating in hobbies or leisure activities, exercising, sexual activity, sleeping, relationships, writing, usual household chores, and enjoyment of life. Each item is scored from 0-10 with a total possible score of 140. Validity was tested for the interference with activity scale ($t=4.81$, $p<.001$), test-retest reliability($r = 0.93$, $P < .001$). Internal consistency was demonstrated using Cronbach's alpha (alpha = .91) (Tofthagen et al., 2011).

Procedures

A nurse practitioner approached potential patients about the study, determined eligibility, explained the risks and benefits, answered questions, and obtained written informed consent.

Participants were in the study for a total of 8 weeks. Patients in the parent study all received acupuncture twice a week for four weeks. The study had a waitlist controlled design and participants provided data at enrollment, four weeks, and eight weeks. Only baseline data were included in this secondary analysis. All study data were collected by a nurse practitioner working on the study, or the principle investigator, who is also a nurse practitioner.

Institutional Review Board Approvals

The parent study was approved by the University of South Florida Internal Review Board (IRB). University of South Florida IRB approval was also obtained for this secondary data analysis.

Data Management and Analysis

This study aimed to evaluate the relationship between the Total Neuropathy Score-reduced and patients' function, as measured by the interference scale of the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool. It also aimed to evaluate the relationship between the Total Neuropathy Score-reduced and neuropathy symptom experience, as measured by the symptom experience scale of the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool.

To achieve these aims, secondary data analysis was done for data obtained from Dr. Tofthagen (PI). Baseline data from this study involving 56 cancer patients were used. Data were kept in a passcode secured cloud account, and the passcode was not shared with any one. Data were de-identified, cleaned as needed and screened for outliers and missing data.

Data analysis was conducted using the Software Package for the Social Sciences version 24. The sample was described using means, standard deviations, frequencies, and

percentages. Total scores on the TNSr, CIPNAT symptom experience scale and CIPNAT interference scale were calculated. To address Aim 1, to evaluate the relationship between the Total Neuropathy Score-reduced and patients' function, as measured by the interference with activity scale of the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool, correlations between total scores on the TNSr and total scores on the interference scale of the CIPNAT were calculated.

To address Aim 2, to evaluate the relationship between the Total Neuropathy Score-reduced and neuropathy symptom experience, as measured by the symptom experience scale of the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool, correlations between total scores on the TNSr and total scores on the symptom experience scale of the CIPNAT were calculated.

CHAPTER FOUR: RESULTS

This Chapter presents the statistical results of the analysis in three parts. The first part presents the demographic characteristics of the sample, including the age, gender, marital status, total years of education, race, and employment status. The second part presents the total scores of the TNSr and the CIPNAT; their means and standard deviation (SD). The third part presents the correlations between the TNSr, CIPNAT, interference scale of the CIPNAT, and symptom experience scale of the CIPNAT.

Demographics

The participants' ages ranged from 40 to 86 years old with a mean of 65 and SD of 10.2. They were about 70% females, 60% married, and all of them had at least 12 years of formal education. Eighty nine percent were white while the rest were minorities. About half of them were retired and one fourth still working full time. The percentage of participants with GI malignancies was 21.7 % and with breast cancer 37%. About half of the participants received a taxane (48.2%), and 35.7% received platinum based chemotherapy, either cisplatin or oxaliplatin (Table 2).

Table 2. Frequencies and percentages for gender, marital status, years of education, race, and employment status. (n=56)

		Frequency	Percentage
Gender	Male	17	30.4
	Female	39	69.6
Marital Status	Single	7	12.5
	Married/Partnered	34	60.7
	Divorced	10	17.9
	Separated	1	1.8
	Widowed	3	5.4
Years of education	12	23	41.1
	13	2	3.6
	14	12	21.4
	15	1	1.8
	16	12	21.4
	18	3	5.4
	19	1	1.8
	20	1	1.8
Race	Asian	2	3.6
	African American	2	3.6
	Hispanic	2	3.6
	White/ Caucasian	50	89.2
Employment Status	Full Time	13	23.2
	Part Time	2	3.6
	On Leave	2	3.6
	Retired	32	57.1
	Disabled	6	10.7
Type of cancer	GI	12	21.4
	Breast	21	37.5
	GYN	3	5.4
	Prostate/Testicular	5	7.1
	Lung	5	8.9
	Lymphoma	3	5.4
	Other	8	14.3
Type of chemotherapy	Taxane	27	48.2
	Platinum	20	35.7
	Vinca	3	5.4
	Multiple	6	10.7

Table 3.Scores of the Study Instruments

	n	Range	Mean	Std. Deviation
TNSr (total score)	56	2-14	7.9286	3.12094
Symptom Experience Scale of the CIPNAT	53	24-279	152.2830	59.95812
Interference with Activity Scale of the CIPNAT	52	0-114	57.6923	33.27281

Scores of the Study Instruments

Total score of the TNSr ranged from 2 to 14.00 (0-20 possible scores) with a mean of 7.92 (SD 3.12). Scores on the symptom experience scale of the CIPNAT ranged from 24 to 279 (0-279 possible scores) with a mean of 152.2 and (SD 59.9), while scores on the interference scale of the CIPNAT ranged from 0 to 114 (0-140 possible scores) with a mean of 57.6 (SD 3.2)

The Correlation between the TNSr, the CIPNAT, Patients' Function, and Neuropathy Symptom Experience

All correlations between the total scores of the study instruments were positive and significant. The correlation between the total scores of the TNSr and the total scores of the CIPNAT was weak and significant ($r=.32$, $P<0.05$). The TNSr total scores were weakly correlated with the neuropathy symptom experience scale ($r=.344$, $P<0.01$), while the correlation between the total TNSr and the interference with activity scale was weak ($r=.289$, $P<0.05$).

Higher correlations were identified between the symptom extension item of the TNSr and the two CIPNAT subscales. The correlation with the symptom experience scale of the

CIPNAT was r=.355 (p<0.01), while the correlation between the symptom extension item of the TNSr and interference with activity scale of the CIPNAT was r=.412, p<0.01). The correlations of the rest of individual TNSr physical exam items with the CIPNAT scales were weak (Table 4).

Table 4. Pearson correlations between the individual items of the TNSr, CIPNAT (total scores), symptom experience scale of the CIPNAT, and Interference with Activity Scale of the CIPNAT.

		CIPNAT (Total Score)	Symptom Experience Scale of the CIPNAT	Interference with Activity Scale of the CIPNAT
Symptom	Pearson Correlation	.395**	.355**	.412**
Extension	Sig. (1-tailed)	.002	.005	.001
	n	50	53	52
Pin Sensibility	Pearson Correlation	.050	.141	-.009
	Sig. (1-tailed)	.366	.157	.476
	n	50	53	52
Vibration	Pearson Correlation	.080	.061	.095
Sensibility	Sig. (1-tailed)	.289	.332	.251
	n	50	53	52
Muscle	Pearson Correlation	.297*	.296*	.311*
Strength	Sig. (1-tailed)	.018	.016	.012
	n	50	53	52
Deep Tendon	Pearson Correlation	.154	.191	.105
Reflexes	Sig. (1-tailed)	.143	.086	.229
	n	50	53	52
TNSr (total score)	Pearson Correlation	.320*	.344**	.289*
	Sig. (1-tailed)	.012	.006	.019
	56	50	53	52

**. Correlation is significant at the 0.01 level (1-tailed).

*. Correlation is significant at the 0.05 level (1-tailed).

CHAPTER FIVE: DISCUSSION

This Chapter discusses the findings of CIPN instruments, the relationship between the TNSr and the CIPNAT and its subscales. Study strengths and limitations, future research and clinical application are also discussed.

One of the main goals for evaluating CIPN assessment instruments is to find instruments that can be easily used in the oncology clinical setting, but provide adequate understanding of the diverse aspects of CIPN. Despite the decades-long research and the creation of multiple instruments, this study did not yield an instrument that can meet the requirements of easy usage and comprehensiveness. These study findings are similar to the few studies comparing objective and subjective instruments (Alberti et al., 2014; Briani et al., 2013; da Silva Simao et al., 2014; Pereira et al., 2016; Reddy et al., 2016; Sharma et al., 2015).

The Findings of CIPN Instruments

It was noted that some participants choose the maximum scores for the items of symptom experience scale of the CIPNAT which is resulted in a total score of 279 explaining the level of their symptoms. Although the time line for chemotherapy treatment to this study assessment was not collected, this is an important factor in the understanding of their symptoms. In some studies, it was noted that some CIPN might improve after six months but some patient may have chronic lingering symptoms resistant to treatment (Argyriou et al., 2005). Although some participants rated their symptom experience at the maximum score, none of them had maximum scores of the TNSr or their interference with activity scores. This is an example of the

incongruence between objective and subjective CIPN instruments. It appears that patients can have severe symptoms with minimal interference with function and without objective evidence of symptoms.

The Relationship between the TNSr and the CIPNAT

In this study, the correlation between the TNSr and the CIPNAT were found to be positive, weak and significant. These results echo similar studies that compared objective and subjective instruments. In a 2013 study, the mean TNSc increased from 1.07 to 5.13 after chemotherapy treatment and 60% of the same sample had documented nerve damage (Briani et al., 2013). In another study, vibration sensation had a positively high moderate correlation with the patient reported quality of life QLQ-CIPN20 (r=0.67) (Sharma et al., 2015). The significant correlation between The TNSr and the CIPNAT makes the prospect of using the TNSr in the clinical oncology setting a reasonable augmentation for the assessment process.

The use of pure subjective or objective CIPN instruments does not yield a perfect understanding of the problem, and apparently neither does combining them (Alberti et al., 2014). There are incongruences between patients' reporting and providers' judgment (Bennett et al., 2012). Therefore, providers should not rely on objective assessment alone, but should incorporate information from patients into their assessment. In addition, the objective instruments are not readily available for the average oncology nurse practitioner or physician.

The Relationship between the TNSr and Patients' Function

In this study, there was a weak correlation between the TNSr and the interference with activity scale of the CIPNAT, which suggests that basic neurologic assessments such as DTRs, vibratory sensation, and pin-prick sensation, all items on the TNSr, are insufficient to

identify difficulties with functioning that patients may be experiencing as a result of CIPN. Cancer treatment can lead to devastating effects on patients' function; thus, a careful assessment before any treatment is needed (Tan, Chamie, Daskivich, Litwin, & Hu, 2016). The effects of CIPN on patients' function led some researchers to consider assessing this function through the prism of CIPN assessment instruments. The CIPNAT interference with activity scale (14 items) is a subjective patient function assessment tool. The Rasch-built overall disability scale for patients with chemotherapy-induced peripheral neuropathy (22 items) is also a subjective instrument that is merely dedicated to the assessment of patient function in the presence of CIPN. While the length of those subjective instruments may discourage the providers from using them in the day-to-day clinical oncologic setting, the objective instruments are not sufficient alone to identify functional impairments or recognize individuals at risk for fall or other injuries.

The Relationship between the TNSr and Neuropathy Symptom Experience

The overall relationship between the TNSr and the symptom experience scale of the CIPNAT was weak. This is the same trend that was seen when relating the TNSr with patients' function. The only item that had slightly higher correlation is the symptom extension as they both measure subjective input of the patients ($r=.35$, $P<.01$). The expansion of this single item to three items, as seen in the TNSr-SF, can be helpful but needs further studying (Lavoie Smith et al., 2011).

Study Strengths and Limitations

Limitations of this study are mainly related to the small sample size. A larger sample might have contributed to more sophisticated analysis techniques including regressions and predictions to better understand the relationships among the study instruments. Regression might have given us further insight on certain items of the instruments leading to compressing those

instruments and making them shorter and easier to use. Also, time line after receiving chemotherapy was not collected; these data are important as CIPN is affected by both chemotherapy type and time after chemotherapy treatment. Participants in this study all were required to have at least moderate neuropathy, which developed following neurotoxic chemotherapy. It is thought that taxane neuropathy improves after two years, but neuropathic pain can linger in a phenomena called coasting, seen mainly with platinums (Izycki et al., 2016). The sample of this study had some participants that received chemotherapy up to 10 years prior to participation, which suggests that this group had neuropathy that did not follow the typical pattern and many in this sample could have been among the approximately 20% of people who will have permanent neuropathy following chemotherapy, or may have had other unknown factors contributing to their neuropathy.

Another limitation is the lack of data regarding inter-rater reliability in this study. Even though a consistent scoring method is used for this objective measure, there is some subjectivity involved with most items on the TNSr, such as reflexes and muscle strength, even when consistent protocols are used, as they were in this study. Evaluation of inter-rater reliability was planned but the ARNP who initially conducted the assessments left the study abruptly. The objective physical exam portion of the TNSr needs to be done consistently by the same trained providers. The reliability of the DTR is questionable when done by multiple clinicians (Binda et al., 2015; Sharma et al., 2009).

Future Research and Clinical Application

Future research involving a larger study sample would help in doing some stratified analysis. It should help in differentiating the findings among different participants with various cancer types, various chemotherapy agent. It is also helpful to differentiate between participants

based on time frame after receiving chemotherapy. The results of this study stress the need to use instruments with subjective patient input as well as providers' objective input.

CONCLUSION

The study found that there is a positive weak relationship between the TNSr and the neuropathy symptoms as measured by the symptom experience scale of the CIPNAT. A positive weak relationship was found between the TNSr and patients' function as measures by the interference with activity scale of the CIPNAT. These results support the need to incorporate patient reported data into CIPN assessment, and do not support the use of clinical evaluation as a superior method of CIPN assessment. The use of assessment instruments needs to be based on the purpose of the assessment and possible interventions. The discipline of nursing, with a focus on alleviating symptoms, prevention of falls, and maintaining a safe environment, must devote significant time and attention to aspects of CIPN assessment that will guide nursing practice. Therefore, healthcare professionals interested in helping patients better control their symptoms or improve their functional status may be better served using subjective instruments such as the CIPNAT. Further research is needed to develop and evaluate instruments that are comprehensive, reliable, valid, and practical for use in clinical settings.

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APPENDIXES

Demographic Data Form

Participant ID:_____

1. What is your current age? _____

2. What is your gender? Male _____ Female _____

3. What is your marital status?
   ____Single
   ____ Married/partnered
   ____ Divorced
   ____ Separated
   ____ Widowed

4. How many years of formal education have you completed? _____
   Example: 12 = high school graduate, 14 = associate degree or technical school, 16 = baccalaureate degree

5. What is your race or ethnicity? (check all that apply)

   _____ American Indian/Alaskan Native
   _____ Asian
   _____ African American
   _____ Hispanic
   _____ Native Hawaiian/Pacific Islander
   _____ White/Caucasian
   _____ Other or Unknown

6. What is your current employment status? (check all that apply)

   _____ Full time employee
   _____ Part time employee
   _____ On leave of absence
   _____ Retired
   _____ Disabled
   _____ Full time student

7. What kind of cancer are you seen at Florida Cancer Specialists for?_____

Description and scoring of TNSr

Score	0	1	2	3	4
Symptom extension	none	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptom extension to knee or elbow	Symptoms above knee or elbow
Pin Sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Vibration Sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Muscle Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Deep Tendon Reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent	All reflexes absent

Chemotherapy Induced Peripheral Neuropathy Assessment Tool (CIPNAT)
Cindy Tofthagen, PhD, ARNP

Directions : Circle your answers to the questions below. Start by answering questions 1-4. If your answer is "yes" to any of the first four questions, please complete the entire questionnaire. If your answer is "no" to all of the first four questions, you may stop. Thank you for completing this evaluation.

Answer B-D for each symptom that you mark as "yes" under A on the left

A Since your chemotherapy, have you developed:			**B** How Severe is it?	**C** How distressing (emotionally upsetting) is it?	**D** How frequently do you have it?
			Not at all Severe … Extremely Severe	Not at all Distressing … Extremely stressing	Never … 100% of the time … always
1. Numbness in the fingers/hands?	no	yes	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
2. Numbness in the toes/feet?	no	yes	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
3. Tingling in the fingers/hands?	no	yes	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
4. Tingling in the toes/feet?	no	yes	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
5. Discomfort in the fingers/hands or toes/feet?	no	yes	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
6. Sensitivity to cold temperature?	no	yes	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
7. Muscle or joint aches?	no	yes	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
8. Weakness in the arms or legs?	no	yes	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
9. Trouble with your balance?	no	yes	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10

Chemotherapy Induced Peripheral Neuropathy Assessment Tool -Abbreviated (CIPNAT-A)
Cindy Tofthagen, PhD, ARNP

How much are the symptoms you reported interfering with:	**Not at all Interfering**										**Completely Interfering**
Dressing (buttoning, zipping, etc)	0	1	2	3	4	5	6	7	8	9	10
Walking	0	1	2	3	4	5	6	7	8	9	10
Picking up objects	0	1	2	3	4	5	6	7	8	9	10
Holding onto objects	0	1	2	3	4	5	6	7	8	9	10
Driving	0	1	2	3	4	5	6	7	8	9	10
Working	0	1	2	3	4	5	6	7	8	9	10
Participating in hobbies or leisure activities	0	1	2	3	4	5	6	7	8	9	10
Exercising	0	1	2	3	4	5	6	7	8	9	10
Sleeping	0	1	2	3	4	5	6	7	8	9	10
Relationships with other people	0	1	2	3	4	5	6	7	8	9	10
Writing	0	1	2	3	4	5	6	7	8	9	10
Usual household chores	0	1	2	3	4	5	6	7	8	9	10
Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

About the Author

Ashraf Abulhaija has over twenty two years of experience as a registered nurse and a nurse practitioner. He specializes in oncology and acute care. He has extensive experience in oncologic acute and urgent care. Currently, he works for Moffitt Cancer Center at the urgent care area treating patients with urgent oncologic and medical issues. He earned his Bachelor of Science degree in Nursing from Jordan University of Science and Technology, Jordan. He has two masters. The first is in Public Administration with interest in health care policy earned from Alalbait University, Jordan. The second is Masters of Science in Nursing (acute care) earned from University of Utah, Utah, USA. He also loves teaching and serves as a volunteer instructor at University of South Florida; College of Nursing. He holds a post-masters certificate in Nursing Education. His research interests are in oncology symptom assessment and management, oncology psycho-sociology, hospital medicine, hospital management, and process improvement.