PHYSICAL THERAPY, EXERCISE AND ACUPUNCTURE FOR THE PREVENTION AND TREATMENT OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY

By

Elizabeth Andersen Hammond

A thesis submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

Human Anatomy and Cell Science, Max Rady College of Medicine,

Rady Faculty of Health Sciences, University of Manitoba

ABSTRACT

Chemotherapy induced peripheral neuropathy can have lasting sensory effects for cancer survivors. At present, the mechanisms causing the neuropathy are unknown and few effective treatment options are available. This thesis includes a review of the literature and four studies. The first study evaluated the potential role for physical therapy and nerve gliding home exercises to improve symptoms of chemotherapy induced peripheral neuropathy (CIPN) and explored whether a dual nerve disorder was present between the surgical and non-surgical side in a population with breast cancer. The nerve gliding exercises had a positive effect on pain as measured by the numeric pain rating scale (NPRS) and pain pressure algometry. No quantitative sensory testing (QST) data could identify a possible dual nerve disorder from surgery combined with chemotherapy. The second trial sought to confirm the effectiveness of electro acupuncture on improving chronic neuropathic pain from CIPN. Electro acupuncture had no positive effect on pain while sham acupuncture significantly improved pain. This trial showed the ineffectiveness of electro acupuncture for chronic CIPN pain symptoms. The third study used the physical therapy study data to define the sensory phenotypes of neuropathic and non-neuropathic symptom profiles. This was completed to identify future targets for mechanism-based treatment. Surprisingly, only left hand heat pain threshold differences were observed on the QST measures. As expected, increased pain (measured by the NPRS) and decreased function (measured by the Disability of the Shoulder, Arm and Hand (DASH)) were observed in the neuropathic group. Using the physical therapy data, the fourth study correlated active participants with preservation of nerve function exploring the possible neuroprotective effect of exercise

on CIPN. ‘Active’ versus ‘less active’ groups revealed significantly improved vibration perception and normalized heat pain thresholds for the active group suggesting possible neuroprotection among exercisers. This thesis helps to direct evidence-based practice and contributes to the literature. Our findings indicate that electro acupuncture should not be pursued as a treatment option for patients experiencing chronic pain from CIPN. Our findings support the use of physical therapy, nerve gliding exercises, and general exercise during and after chemotherapy. Physical therapy and nerve gliding exercises help reduce the symptoms associated with chemotherapy induced peripheral neuropathy while maintaining physical activity throughout treatment may provide neuroprotection.

ACKNOWLEDGEMENTS

Successful completion of this thesis required the assistance and support of many. I have really enjoyed the last 4 years due in large part to my mentor and advisor Dr. Barbara Shay. Thank you for taking me on as a student. I would never have taken this on without your support and guidance. Thank you to my committee, Dr. Tom Klonisch, Dr. Leanne LeClair, and Dr. Marshall Pitz for your time and valuable input. Additionally, thank you Dr. Pitz for being instrumental in recruitment. Without you, Lori Santoro, and Linda Davidson I may still be at an n=2.

Thank you to the CancerCare Manitoba Foundation (CCMF) grant for funding the physical therapy trial, the College of Rehabilitation Sciences (CoRS catalyst grant) and the Physiotherapy Foundation of Canada (Acupuncture Division) for funding the Acupuncture trial.

I have had much help in the development of the physical therapy treatment program from Karen Steinfeld. Thank you for your time and dedication to the participants in the trial. Thank you to Sam Steinfeld for sharing and encouraging my interest in pain science and for literally getting me up and running to start my PhD. Thank you to Janine Didyk who provided the acupuncture treatment.

Finally, this could never have been completed without the support and commitment of the patients and their families. Thank you for giving us your time when you had so many other commitments and priorities.

DEDICATION

To my family

Allan, William, Emma and Mom

and to Barb

LIST OF ABBREVIATIONS

Aα	A alpha (large myelinated fibre)
Aβ	A Beta (myelinated fibre)
Aδ	A delta (thinly myelinated fibre)
ACSM	American College of Sports Medicine
BDNF	brain derived neurotrophic factor (protein binds to TrkB and p75 receptors)
BMI	body mass index
CAM	Complementary Alternative Medicine
CCI	chronic constriction injury
CHD	coronary heart disease
CIPN	chemotherapy induced peripheral neuropathy
CNS	central nervous system
COX-2	cyclooxygenase-2 (enzyme elevated during inflammation)
DASH	disability of the shoulder, arm, and hand
DNIC	descending noxious inhibitory control (pain modulation pathway)
DRG	dorsal root ganglion
EA	electro acupuncture
FECD	5-fluorouracil/epirubicin/cyclophosphamide x3 & Docetaxel 100mg/m2 x 3
GFAP	glial fibrillary acidic protein (protein expressed in the CNS)
HREB	Health Research Ethics Board
HSP-72	heat shock protein (stabilizes proteins in response to stress)
IENF	intra-epidermal nerve fibre (cutaneous receptors and afferents)
IENFD	intra-epidermal nerve fibre density
IL	interleukin (cytokine, protein and signaling molecule in immune system)
IQR	interquartile range
Kpa	kilopascals
LI4	acupuncture point on hand
LR3	acupuncture point on foot
LTM	low threshold mechanoreceptors
MAPK	mitogen-activated protein kinase
MCID	minimum clinical important difference
METS	metabolic equivalents
mPTP	mitochondrial permeability transition pore
NCS	nerve conduction studies
NGF	nerve growth factor
NMDAR	N-methyl-D-aspartate receptor
NO	nitric oxide (free radical)
NPRS	numeric pain rating scale
NT-3	neurotrophin 3 (neuron protein growth factor)
OX-42	antibody recognizing CR3 complement receptor for microglia
PAG	periaqueductal gray
PKC	protein kinase C
PRL	pain research labratory
QOL	quality of life
QST	quantitative sensory testing

RCT	randomized controlled trial
ROM	range of motion
ROS	reactive oxygen species
RVM	rostral ventralmedial medulla
S-LANSS	Self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs
SFN	small fibre neuropathy
ST-36	acupuncture point on lower leg
STRICTA	Standards for Reporting Interventions in Clinical Trials of Acupuncture
TC	docetaxel 75mg/m2 and cyclophosphamide x 4
TIPN	taxane induced peripheral neuropathy
TRP	transient receptor potential
TRPA1	transient receptor potential ankyrin 1
TRPV1	transient receptor potentials vanilloid 1
TSA	thermal sensory analyzer
VAS	visual analog scale
VSA	vibration sensory analyzer
WHO	World Health Organization

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

According to Canadian cancer statistics, 1 in 2 Canadians are expected to get cancer in their lifetime. Breast cancer is the third most common cancer and the leading cancer for women (25%). The net 5 year survival rates for breast cancer are improving and currently estimated at 87% (CCS and Stats Can, 2018). Taxanes, a group of chemotherapeutics (including Docetaxel and Paclitaxel), are widely used drugs in the treatment of breast and many other cancers. A major adverse effect with the use of taxanes is taxane induced peripheral neuropathy (TIPN) affecting an estimated 80-97% of patients (Kerckhove et al., 2017).

The etiology of TIPN is still unclear; however, taxanes are microtubule-stabilizing agents that prevent division of cells (E. Gornstein & Schwarz, 2014; Grisold, Cavaletti, & Windebank, 2012). Healthy peripheral nerves are thought to be damaged by microtubule stability (E. L. Gornstein & Schwarz, 2017; Seretny et al., 2014). Both positive (spontaneous pain, heightened sensitivity with light touch, tingling, itching, burning) and negative sensory symptoms (loss of touch, loss of hot/cold sensations and loss of pain) are experienced in the hands and feet, worsening with increasing dose and treatment duration. A retrospective study found that 10% of patients on Docetaxel or Paclitaxel had a dose reduction or interruption during treatment because of Chemotherapy induced peripheral neuropathy (CIPN) symptoms (Speck et al., 2013). While many patients experience transient CIPN symptoms that resolve once the chemotherapy treatment has completed, studies estimate between 25-60% will experience lasting neuropathic symptoms for months to years after the completion of chemotherapy (Hershman et al., 2011; Park et al., 2011).

CIPN is specifically a small fibre sensory neuropathy (SFN) affecting the Aδ fibre, C-fibre and Aβ fibres. These fibres are primarily responsible for transmitting thermal detection (warm and cool), thermal pain (hot and cold), light touch and vibration sense. Either positive or negative sensory symptoms or both can occur resulting in a variety of symptoms including pain (stabbing, burning, shooting), tingling, pins and needles, loss of sensation with numbness, and altered perceptions of sensation with allodynia (pain perceived with a non-painful stimulus), and hyperalgesia (increased sensitivity to a stimulus). Nerve conduction studies (NCS) are normal during the early stages of the axonopathy since they only monitor the amplitude and velocity of large Aα fibres.

Quantitative sensory testing (QST) are a variety of non-invasive tests used in research to clinically assess and quantify sensory perceptions (Boyette-Davis et al., 2013; Hershman et al., 2011; Park et al., 2011; Walk et al., 2009). QST is used for sensory detection and pain thresholds for both mechanical and thermal stimuli. It is valuable in quantifying neuropathic pain and identifying sensory phenotypes for mechanism-based pain treatment (Krumova, Geber, Westermann, & Maier, 2012). Light touch threshold communicates the lower limits of mechanical pressure on the skin, activating Merkels and Meissner corpuscles (low-threshold mechanoreceptors LTM's) transmitted by Aβ fibres. Increased sensitivity to light touch can result in mechanical allodynia. Vibration perception activates Pacinian corpuscles, also mediated by Aβ fibres. Deep pressure threshold, measured by pressure algometry, stimulates intramuscular afferents and can be used as a measure of central sensitization when used at a point distant from the site of pain. Aδ fibres transmit cool detection threshold, while warm detection threshold is transmitted by C-fibres. Both noxious heat and

noxious cold transmit via C-fibre and Aδ fibres. An increased sensitivity to thermal pain thresholds indicates thermal hyperalgesia while loss of thermal pain response indicates hypoesthesia. Currently, there is no gold standard test for diagnosing SFN; however, a normal NCS and abnormal QST will confirm the diagnosis (Hoeijmakers, Faber, Lauria, Merkies, & Waxman, 2012; Lauria, 2005).

Identified risk factors include advanced age, previous chemotherapy, exposure to toxins, and genetic disorders known to cause peripheral neuropathic symptoms (Grisold et al., 2012). These factors can predispose the patient to more severe symptoms of the neuropathy. One potential risk factor that has been mentioned, but not studied, is pre-existing nerve health that may sensitize the nerve to further injury with the chemotherapy drug. (Schmid & Coppieters, 2011; Stubblefield, McNeely, Alfano, & Mayer, 2012).

Treatments to date have focused mainly on pharmacological interventions for neuropathic pain, with little success. A 2014 practice guideline from the American Society for Clinical Oncology identifies that no agents can be recommended to prevent chemotherapy induced peripheral neuropathy (CIPN), and only moderate support for treatment with a serotonin-norepinephrine re-uptake inhibitor, duloxetine (Hershman et al., 2014; Smith et al., 2013; Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007). Unfortunately, duloxetine is associated with common side effects (nausea, insomnia, and dizziness), and a physician must closely monitor drug dosage. Smith and colleagues report that it may be more effective in treating oxaliplatin rather than taxane CIPN neuropathic symptoms (Smith et al., 2013). An evidence-based consensus statement of expert opinion from the Canadian Pain Society was developed after review

of the literature for pharmacological management of neuropathic pain in order to provide guidelines for treatment. Authors state that physical therapy programs, exercise, and psychological treatment are needed in conjunction with duloxetine to optimize successful outcomes (Moulin et al., 2014).

To summarize, at present, CIPN symptoms cannot be prevented or appropriately treated and are a significant burden for patients post chemotherapy. With many cancers being successfully managed by current medical and surgical advances, it is essential to identify and target the residual side effects that may affect quality of life.

This thesis seeks to explore if physical therapy, acupuncture and exercise can offer either neuroprotection or treatment of symptoms for patients with breast cancer exposed to taxanes and classify whether distinct differences in sensory phenotypes between neuropathic and non-neuropathic symptoms exist in this population. Two separate clinical trials for physical therapy and acupuncture were designed to study taxane induced peripheral neuropathy (TIPN). Two additional descriptive studies were planned that could be addressed from the physical therapy trial data. The first used the Self report version of the Leeds Assessment for Neuropathic Symptoms and Signs (S-LANSS) to divide neuropathic and non-neuropathic sensory phenotypes of CIPN to add to the mechanism-based pain management literature. The second divided participants who were ‘active’ throughout treatment for breast cancer versus those ‘less active’ to explore further a possible neuroprotective effect of exercise. Outcome measures included the use of quantitative sensory testing (QST) and self-report questionnaires to define the sensory neuropathy in all four studies.

To begin, chapter 2 is a review of the literature on the pathophysiology of taxane induced peripheral neuropathy (TIPN), neuropathic pain, and the evidence for exercise. Chapter 3 explores physical therapy and nerve gliding exercises for the treatment of chemotherapy induced peripheral neuropathy. Chapter 4 evaluates the effectiveness of electro acupuncture for chronic neuropathic pain caused by taxane induced peripheral neuropathy. Chapter 5 explores the sensory phenotypes of neuropathic and non-neuropathic QST sensory profiles to attempt to identify targets for mechanism-based pain management. Chapter 6 describes the QST sensory profiles of those who remained ‘active’ throughout breast cancer treatment and those ‘less active’ to explore the neuroprotective effect of exercise on TIPN. Chapter 7 summarizes the findings and conclusions.

REFERENCES

Boyette-Davis, J. A., Cata, J. P., Driver, L. C., Novy, D. M., Bruel, B. M., Mooring, D. L., . . . Dougherty, P. M. (2013). Persistent chemoneuropathy in patients receiving the plant alkaloids paclitaxel and vincristine. *Cancer chemotherapy and pharmacology, 71*(3), 619-626. doi:10.1007/s00280-012-2047-z; 10.1007/s00280-012-2047-z

Gornstein, E., & Schwarz, T. L. (2014). The paradox of paclitaxel neurotoxicity: Mechanisms and unanswered questions. *Neuropharmacology, 76 Pt A*, 175-183. doi:10.1016/j.neuropharm.2013.08.016; 10.1016/j.neuropharm.2013.08.016

Gornstein, E. L., & Schwarz, T. L. (2017). Neurotoxic mechanisms of paclitaxel are local to the distal axon and independent of transport defects. *Experimental neurology, 288*, 153-166. doi:S0014-4886(16)30400-9 [pii]

Grisold, W., Cavaletti, G., & Windebank, A. J. (2012). Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro-oncology, 14 Suppl 4*, iv45-54. doi:10.1093/neuonc/nos203; 10.1093/neuonc/nos203

Hershman, D. L., Lacchetti, C., Dworkin, R. H., Lavoie Smith, E. M., Bleeker, J., Cavaletti, G., . . . American Society of Clinical, O. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 32*(18), 1941-1967. doi:10.1200/JCO.2013.54.0914; 10.1200/JCO.2013.54.0914

Hershman, D. L., Weimer, L. H., Wang, A., Kranwinkel, G., Brafman, L., Fuentes, D., . . . Crew, K. D. (2011). Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. *Breast cancer research and treatment, 125*(3), 767-774. doi:10.1007/s10549-010-1278-0; 10.1007/s10549-010-1278-0

Hoeijmakers, J. G., Faber, C. G., Lauria, G., Merkies, I. S., & Waxman, S. G. (2012). Small-fibre neuropathies--advances in diagnosis, pathophysiology and management. *Nature reviews.Neurology, 8*(7), 369-379. doi:10.1038/nrneurol.2012.97; 10.1038/nrneurol.2012.97

Kerckhove, N., Collin, A., Conde, S., Chaleteix, C., Pezet, D., & Balayssac, D. (2017). Long-Term Effects, Pathophysiological Mechanisms, and Risk Factors of Chemotherapy-Induced Peripheral Neuropathies: A Comprehensive Literature Review. *Frontiers in pharmacology, 8*, 86. doi:10.3389/fphar.2017.00086 [doi]

Krumova, E. K., Geber, C., Westermann, A., & Maier, C. (2012). Neuropathic pain: is quantitative sensory testing helpful? *Current diabetes reports, 12*(4), 393-402. doi:10.1007/s11892-012-0282-7; 10.1007/s11892-012-0282-7

Lauria, G. (2005). Small fibre neuropathies. *Current opinion in neurology, 18*(5), 591-597.

Moulin, D., Boulanger, A., Clark, A. J., Clarke, H., Dao, T., Finley, G. A., . . . Williamson, O. D. (2014). Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain research & management : the journal of the Canadian Pain Society = journal de la societe canadienne pour le traitement de la douleur, 19*(6), 328-335.

Park, S. B., Lin, C. S., Krishnan, A. V., Friedlander, M. L., Lewis, C. R., & Kiernan, M. C. (2011). Early, progressive, and sustained dysfunction of sensory axons underlies paclitaxel-induced neuropathy. *Muscle & nerve, 43*(3), 367-374. doi:10.1002/mus.21874; 10.1002/mus.21874

Schmid, A. B., & Coppieters, M. W. (2011). The double crush syndrome revisited--a Delphi study to reveal current expert views on mechanisms underlying dual nerve disorders. *Manual therapy, 16*(6), 557-562. doi:10.1016/j.math.2011.05.005 [doi]

Seretny, M., Currie, G. L., Sena, E. S., Ramnarine, S., Grant, R., MacLeod, M. R., . . . Fallon, M. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain, 155*(12), 2461-2470. doi:10.1016/j.pain.2014.09.020; 10.1016/j.pain.2014.09.020

Smith, E. M., Pang, H., Cirrincione, C., Fleishman, S., Paskett, E. D., Ahles, T., . . . Alliance for Clinical Trials in, O. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *Jama, 309*(13), 1359-1367. doi:10.1001/jama.2013.2813; 10.1001/jama.2013.2813

Speck, R. M., Sammel, M. D., Farrar, J. T., Hennessy, S., Mao, J. J., Stineman, M. G., & DeMichele, A. (2013). Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in nonmetastatic breast cancer. *Journal of oncology practice / American Society of Clinical Oncology, 9*(5), e234-240. doi:10.1200/JOP.2012.000863; 10.1200/JOP.2012.000863

Stubblefield, M. D., McNeely, M. L., Alfano, C. M., & Mayer, D. K. (2012). A prospective surveillance model for physical rehabilitation of women with breast cancer: chemotherapy-induced peripheral neuropathy. *Cancer, 118*(8 Suppl), 2250-2260. doi:10.1002/cncr.27463; 10.1002/cncr.27463

Visovsky, C., Collins, M., Abbott, L., Aschenbrenner, J., & Hart, C. (2007). Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. *Clinical journal of oncology nursing, 11*(6), 901-913. doi:10.1188/07.CJON.901-913

Walk, D., Sehgal, N., Moeller-Bertram, T., Edwards, R. R., Wasan, A., Wallace, M., . . . Backonja, M. M. (2009). Quantitative sensory testing and mapping: a review of nonautomated quantitative methods for examination of the patient with neuropathic pain. *The Clinical journal of pain, 25*(7), 632-640. doi:10.1097/AJP.0b013e3181a68c64; 10.1097/AJP.0b013e3181a68c64

CHAPTER 2: Neuropathic Pain in Taxane Induced Peripheral Neuropathy: Evidence for exercise in treatment

Running Head: Taxane Induced Peripheral Neuropathy (TIPN) and evidence for exercise

MY CONTRIBUTION TO THE MANUSCRIPT

The development of this review forms a portion of my candidacy paper. I completed the literature search. The editing was a joint collaboration between Dr. Barbara Shay and myself. This section is prepared for publication in a peer reviewed journal.

ABSTRACT

One in two Canadians is expected to get cancer in their lifetime (Global Burden of Disease Cancer et al., 2017). Many cancers including breast, ovarian and lung cancer are treated using taxane chemotherapy with curative intent. A major adverse effect with the use of taxane chemotherapeutic agents is taxane induced peripheral neuropathy (TIPN). Both positive (spontaneous pain, heightened sensitivity with light touch, tingling, itching, burning) and negative (loss of touch, loss of hot/cold sensations and loss of pain) sensory symptoms can be experienced in the hands and feet, and worsen with increasing dose and treatment duration. The pathophysiology of TIPN is still unknown but likely involves multiple mechanisms including microtubule impairment, neuro-immune and inflammatory changes, ion channel remodeling, impaired mitochondrial function, and genetic predisposition (Kerckhove et al., 2017; Starobova & Vetter, 2017). This review highlights current theories on the pathophysiology for TIPN, the cellular responses thought to maintain neuropathic pain and the importance of exercise in cancer prevention, rehabilitation, and treatment of neuropathic pain.

KEY WORDS: chemotherapy induced peripheral neuropathy (CIPN), neuropathic pain, exercise, rehabilitation

PATHOPHYSIOLOGY

The etiology of taxane induced peripheral neuropathy (TIPN) is still unclear; however, taxanes are microtubule-stabilizing agents that prevent division of cells (E. Gornstein & Schwarz, 2014; Grisold, Cavaletti, & Windebank, 2012). Taxanes bind with high affinity to the interior portion of the b-tubulin subunit of the microtubule which suppresses dynamic stability, and thus stops mitosis. While this is effective to arrest rapidly dividing tumor cells, the same action is thought to affect healthy peripheral nerves. Microtubules require dynamic stability and act as scaffolding for molecular motors to transport nutrients, neurotransmitters, mitochondria from the cell body to the periphery via anterograde transport. Used synaptic vesicles and other proteins for degradation return to the cell soma via retrograde transport. Loss of microtubule dynamic stability results in loss of transport function. Microtubules are also critical in directing the growth cone and filipodia which advance neuron outgrowth. Impairment to the function of the microtubules and breakdown of the transport process and has been implicated in causing changes in the morphology and physiology of the peripheral nerve. The results are described as a slow wallerian type distal axonopathy that moves more proximally with increasing dose and duration of chemotherapy treatment. It is thought that longer nerves are more vulnerable to impaired transport, and this theory has been used to explain the distal axonopathy as well as the phenomenon of ‘coasting’. Coasting is the term used to describe progressive worsening of TIPN symptoms after chemotherapy. It is thought to be related to the time required for anterograde transport to move the chemotherapy drug from the dorsal root ganglion (DRG) to the distal axon (Bennett, Liu, Xiao, Jin, & Siau, 2011; Han & Smith, 2013;

Kerckhove et al., 2017; Sisignano, Baron, Scholich, & Geisslinger, 2014; Starobova & Vetter, 2017).

Recent research by Gornstein and Swartz suggests paclitaxel locally impacts microtubules in the distal axon and transport deficits may not be the primary cause. The authors applied paclitaxel (10-50nm) to the mid and distal axon of adult mouse DRG neurons and found the distal portion to be selectively sensitive, while the mid axon portion showed no significant changes compared to control. Specifically, the authors suggest that paclitaxel disrupts growth cone dynamics in filipodial extension of pioneer microtubules in the sensory nerve. Pioneer microtubules are active and in a high metabolic state maintaining retraction and advancement of the nerve as the epithelium regenerates; therefore, stabilization of these pioneer microtubules would directly result in impairment at the distal axon (E. L. Gornstein & Schwarz, 2017). Other suggested primary mechanisms of TIPN include mitotoxicity (swollen and vaculated mitochondria) that are present in Aδ and C fibres after chemotherapy resulting in Ca2+ release (opening mitochondrial permeability transition pore (mPTP) and neuronal excitability). Damaged cellular function leads to an increase in reactive oxidative stress (ROS), subsequent ion channel changes (TRPV1 via PKC or MAPK), release of inflammatory cytokines, and activation of caspase 3/7 (Kerckhove et al., 2017; Miltenburg & Boogerd, 2014; Starobova & Vetter, 2017; Xiao, Zheng, & Bennett, 2012). This may, in part, be related to a second low affinity binding site of taxanes to the end of the microtubules associated with generating mediators of inflammation (IL, NO and COX-2) (Fitzpatrick & Wheeler, 2003).

The clinical presentation of TIPN is reported as a terminal nerve ending sensory disturbance with increased vibration perception and loss of temperature sensation (Gutierrez-Gutierrez, Sereno, Miralles, Casado-Saenz, & Gutierrez-Rivas, 2010). This small fibre sensory neuropathy specifically affects the Aδ (thinly myelinated fibres involved in cold perception and thermal pain), C-Fiber (un-myelinated fibres involved in warm temperature perception and thermal pain) and the Aβ fibres (myelinated fibres involved in touch and vibration sense). Nerve conduction studies are normal during the early stages of the axonopathy since they monitor the amplitude and velocity of large myelinated fibres. Skin biopsy, quantification of intraepidermal nerve fibre density (IENF), and quantitative sensory testing (QST) are useful in diagnosing and monitoring this neuropathy. Currently, there is no gold standard test for diagnosing small fibre neuropathy; however, in the presence of symptoms mentioned above with abnormal QST and a normal nerve conduction study will confirm the diagnosis (Hoeijmakers, Faber, Lauria, Merkies, & Waxman, 2012; Lauria, 2005).

Large interpersonal variability exists in neuropathy location (hands or feet) and intensity of symptoms. This has been explained by variability in chemotherapy cumulative dose, schedule, combination therapy, pre-existing risk factors (including diabetes, advanced age, smoking, increased alcohol consumption), increased body mass index (BMI) and genetic predisposition (Cioroiu & Weimer, 2017; Eckhoff, Feddersen, Knoop, Ewertz, & Bergmann, 2015; Kandula et al., 2017; Kus et al., 2016). The presence of cold allodynia and cold hyperalgesia during chemotherapy has been clinically identified as a risk factor for persistent TIPN symptoms (Seretny et al., 2014).

A retrospective study found that 10% of patients on Docetaxel or Paclitaxel had a dose reduction or treatment delay during treatment because of TIPN symptoms (Speck et al., 2013). Other studies have estimated that 25-60% of all patients will experience lasting neuropathic symptoms months to years after the completion of chemotherapy (Hershman et al., 2011; S. B. Park et al., 2011). The monetary burden of chemotherapy induced peripheral neuropathy (CIPN) has been estimated to cost over seventeen thousand per person per year in the United States (Pike, Birnbaum, Muehlenbein, Pohl, & Natale, 2012), and is associated with anxiety, sleep disorders and depression (Hong, Tian, & Wu, 2014).

Reviews have summarized potential treatment approaches studying anti-oxidants, vitamins and herbal medicines such as Goshajinkigan, Acetyl-L-carnitine, Ca2+-Mg2+ infusions, Vitamin A, B and E (Han & Smith, 2013; Poupon et al., 2015; Sisignano et al., 2014; Wing et al., 2017). These potential treatments have shown promise for possible preventative management by reducing oxidative stress in cell research and animal models. A few of these studies have led to clinical trials; however, they failed to produce either neuroprotection or alleviation of symptoms (Hershman et al., 2013; Poupon et al., 2015).

At present, expert opinion from the 2014 practice guidelines from the American Society for Clinical Oncology has indicated that no agents can be recommended to prevent CIPN and provides only moderate support for treatment with a serotonin-norepinephrine re-uptake inhibitor, duloxetine (Hershman et al., 2014; Smith et al., 2013; Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007). Unfortunately, duloxetine is associated with side effects (nausea, insomnia, and dizziness), and a

physician must closely monitor drug dosage. Further, duloxetine may be more effective in treating oxaliplatin symptoms rather than taxane neuropathic symptoms (Smith et al., 2013). In a consensus statement from the Canadian Pain Society, it has been identified that physical therapy programs, exercise, and psychological treatment are needed in conjunction with duloxetine to optimize successful outcomes (Moulin et al., 2014).

In addition to Duloxetine, topical agents have been commonly suggested for treatment of symptoms. Results from clinical trials regarding sensory symptom improvement are mixed. A phase III six week trial of topical ketamine and amitriptyline demonstrated no improvement in pain scores (Gewandter et al., 2014). Another randomized controlled trial used a topical combination of ketamine, amitriptyline, and baclofen demonstrating improved tingling sensory subscales but not numbness, thermal or functional improvements (Barton et al., 2011). Topical menthol has been suggested as a possible treatment but requires further study (Fallon et al., 2015).

There is a theory that a single pharmacological treatment may be possible for all chemotherapy induced peripheral neuropathy (CIPN) due to similar overlapping mechanisms of mitotoxicity. Oxaliplatin, cisplatin, vincristine, and paclitaxel all have mitotoxicity as part of the pathophysiology (Xiao et al., 2012). It has been postulated that this may involve inhibiting TRPV1 or NMDAR activation with additional anti-inflammatory properties, perhaps by inhibiting p38-MAPK (Sisignano et al., 2014).

One of the major concerns of targeting the pathway to prevent or minimize TIPN is that it also could theoretically affect taxane drug efficacy (Cioroiu & Weimer, 2017). Thus, it is important to find a treatment that can block TIPN or restore sensory function that is independent from the chemotherapy pathway.

MECHANISMS MAINTAINING NEUROPATHIC PAIN

Depending on the chemotherapy agent severity of symptoms can vary. Platinum-based drugs, specifically oxaliplatin, can cause acute severe sensory disturbances immediately following chemotherapy administration and is thought to be the most neurotoxic of all the drugs with lasting chronic symptoms up to 25 years. By comparison, taxane drug neurotoxicity is as prevalent as the platinum-based drugs affecting 80-97% of patients but the lasting symptoms are thought to be less severe with a reported 4.75 years maximum duration. Of the taxane drugs, paclitaxel neuropathy symptoms are reportedly more severe and persistent when compared to docetaxel (Kerckhove et al., 2017).

TIPN has two main sensory phenotypes. One is loss of sensation (or a negative sensory profile) that is generally associated with the loss of IENFD fibres, loss of myelination, and dying back of the sensory axon. The second is associated with hypersensitivity (or a positive sensory profile) potentially caused by an increased number of ion channels, altered or impaired Ca2+ signaling, neuro inflammation, and activation of adjacent silent nociceptors. Neuropathic pain is part of the positive sensory symptom profile of TIPN and includes sensations of stabbing, burning, shooting, tingling, allodynia, hyperalgesia, and pins and needles. These symptoms are thought to be maintained by peripheral and central sensitization (Brewer, Morrison, Dolan, & Fleming, 2016; Grisold et al., 2012; Kerckhove et al., 2017).

Since taxanes do not cross the blood brain barrier, spinal cord and central involvement are thought to originate from information provided from peripheral afferent input. Maintaining neuropathic pain potentially may arise initially from peripheral

nociceptive input to the spinal cord. Chemotherapy induces mitochondrial damage which directly contributes to abnormal spontaneous discharge of Aδ and C-fibres with mechano and thermal hypersensitivity via TRPA1 (mechano and cold sensitivity) and TRPV1 (heat hyperalgesia) receptors at the distal terminal sensory ending (Xiao et al., 2012). This distal axon mitotoxicity could be the cause of peripheral nociceptive input that would explain the sequence of events leading to spontaneous nerve firing (shooting pain), sensitized receptors (cold and hot hyperalgesia), and release of pro-inflammatory cytokines (allodynia and neuro-inflammation) (Bennett et al., 2011; Doyle et al., 2012; Xiao et al., 2012). Constant peripheral input or impaired processing can maintain spinal cord dorsal horn excitability (glia cell activation) resulting in cortical changes, central sensitization, and impaired descending noxious inhibitory control (DNIC) (Haroutounian et al., 2014; Lundborg, 2000; Rosen, Bjorkman, & Lundborg, 2006; Yarnitsky et al., 2008). Activated glia (microglia and astrocytes) at the dorsal horn seem to be central in maintaining neuropathic pain, increasing pro-inflammatory cytokines, and brain derived neurotrophic factor (BDNF) (Dobson, McMillan, & Li, 2014).

ANIMAL MODELS OF EXERCISE AND NEUROPATHIC PAIN

To attempt to understand how exercise improves peripheral nerve regeneration and neuropathic pain, animal models have been developed. Chronic constriction injury (CCI) is a common model used to induce neuropathic pain by tying a suture around the sciatic nerve with resultant mechanical allodynia and thermal hyperalgesia. Using these animal pain models, research has shown that aerobic exercise and neural movement

can reduce allodynia (measured by paw withdrawal to von Frey hairs) and thermal hyperalgesia (measured by infrared heat or cold plate withdrawal thresholds).

Armada-da-Silva and colleagues have shown that physical exercise increases both the number of axons and rate of axonal elongation. Additionally, exercise prior to injury may help pre-condition the nervous system to be able to rehabilitate more effectively after injury (Armada-da-Silva, Pereira, Amado, & Veloso, 2013). In a CCI rat model of neuropathic pain, voluntary wheel running before injury suppresses allodynia post-injury (Grace et al., 2016). Ten neural mobilization treatments (a commonly used nerve treatment technique in physical therapy) decreased glial activity (GFAP expression, OX-42 and BDNF immunoreactivity) in the periaqueductal grey (PAG) and thalamic nuclei that are related to maintaining neuropathic pain (Giardini et al., 2017). Swim therapy (1 hour daily for 6 weeks) has been shown to significantly reduce allodynia and hyperalgesia in another rat model of neuropathic pain (Shen, Fox, & Cheng, 2013).

Regular aerobic exercise has been shown to attenuate neuropathic pain mediated by endogenous opioid systems (Stagg et al., 2011). Using a spinal nerve ligation model of neuropathic pain, mechanical and thermal hyperalgesia was reversed within 3 weeks with a five-week forced treadmill training session post-ligation. The positive effects of exercise on neuropathic pain was intensity (not frequency) dependent, and the hypersensitivity returned to pre-exercise levels within 8 days of discontinuing the exercise. Results suggest that maintaining regular exercise of moderate intensity is required to preserve the protective effects. Mechanisms mediating this exercise induced modulation of neuropathic pain is a result of increased

endogenous opioid levels in the PAG and rostral ventralmedial medulla (RVM), and was confirmed using an intracerebroventricular injection of naloxone (Stagg et al., 2011).

A mouse model of TIPN and exercise has been developed (J. S. Park, Kim, & Hoke, 2015). Treadmill exercise began one week prior to paclitaxel and continued 7 days/week for 4 weeks. Daily exercise prevented thermal hyperalgesia, and histological evaluations confirmed that exercise prevented a decrease in unmyelinated axons. The authors conclude that the impact of exercise demonstrates 'a robust neuroprotective effect' and that an upregulation of brain derived neurotrophic factor (BDNF) in motor axons may assist in protecting the sensory axons from the neurotoxic effects of paclitaxel (J. S. Park et al., 2015).

EXERCISE AND CANCER

International guidelines, World Health Organization (WHO) recommendations, and American College of Sports Medicine (ACSM) guidelines reinforce the importance of exercise for general health. It is believed that there is a near linear relationship between the benefits of exercise and health in a dose-dependent manner. A review of evidence-informed guidelines for Canadians identifies that if all Canadians followed current guidelines (30-40 minutes of moderate intensity exercise on most days) deaths could be reduced by 33% for coronary heart disease (CHD), 25% for stroke, 20% for colon cancer, 20% for diabetes, 14% for breast cancer, 20% for hypertension and 25% for osteoporosis (Katzmarzyk & Ardern, 2004; Warburton, Katzmarzyk, Rhodes, & Shephard, 2007). Despite this knowledge, 48% of men and 54% of women are physically inactive in the general population (Warburton et al., 2007).

Cancer specific population estimates reveal higher levels of obesity with lower levels of activity (fewer than 22% are reportedly active). Patient preference for type of exercise, social, cognitive, demographic, environmental and medical variables are all important considerations when prescribing exercise during chemotherapy (Courneya et al., 2008; Rogers, Courneya, Verhulst, Markwell, & McAuley, 2008). Specifics of barriers to exercise that patients report include treatment side effects, time constraints and fatigue. Authors reviewing barriers and facilitators of exercise identify that the barriers reported are often the symptoms that can be improved with exercise (Blaney, Lowe-Strong, Rankin-Watt, Campbell, & Gracey, 2013; Clifford et al., 2018).

For many cancer survivors restoring physical function after diagnosis and treatment is difficult. A prospective breast cancer study (n=267) measuring physical activity confirmed, as expected, that physical activity declines significantly post-operatively. Activity levels measured included occupation, sport and household activity, as well as an overall activity measure. Follow up at one year found that these women had not returned to their pre-operative physical activity levels (Devoogdt et al., 2010).

Physical activity during and after medical treatment is important to maintain and improve cardiovascular fitness, muscle strength, balance, flexibility and range of motion, reduce fatigue, depression, and generally improve quality of life (Baumann et al., 2013; Hayes et al., 2012; Streckmann, Kneis, et al., 2014; Streckmann, Zopf, et al., 2014). Moderate intensity exercise improves musculoskeletal fitness and positive mental health (including reduced rates of both depression and anxiety) that are extremely important to maximize quality of life (Warburton et al., 2007). Possible mechanisms for improved health with exercise include lower serum concentrations of sex hormones, improved

insulin sensitivity, reduction in systemic inflammation, and improved immune function (McTiernan, 2008). A cochrane review specific to exercise and breast cancer found moderate support that exercise can lessen fatigue and improve physical fitness, cancer specific quality of life measures, and cognitive function (Furmaniak, Menig, & Markes, 2016). Physical activity literature specific to cancer identify that a reduction of adipose tissue, reduction in circulating hormones, lower production of insulin, reduction of reactive oxygen species (ROS), and other inflammatory markers with natural killer cell activation may be possible mechanisms that might reduce cancer risk or recurrence (Knop et al., 2011; McTiernan, 2008; Zimmer et al., 2015).

The clinical oncology society of Australia recently published a position statement on exercise in cancer care. Their recommendations advocate all members of the oncology team to support exercise for patients. When possible the current guidelines (150 minutes of moderate activity or 75 minutes of high intensity aerobic activity and at least 2-3 resistance training sessions weekly) should be encouraged in order to reduce cancer related side effects and disease burden. While clinical trials and epidemiological data have correlated physical activity to improved disease free and overall survival, larger phase III studies are required to confirm this association (Cormie et al., 2018; Courneya et al., 2014).

EXERCISE AND PERIPHERAL NEUROPATHY

Exercise has anti-inflammatory effects on the nervous system that may be critical in understanding how exercise can attenuate symptoms of neuropathic pain. Decreasing pro-inflammatory cytokines, normalizing glial cell activation and BDNF, and

upregulating other neurotrophic factors along with many other proposed mechanisms are being revealed in experimental studies (Cooper, Kluding, & Wright, 2016).

A recent systematic review on exercise intervention and peripheral neuropathy identified 18 clinical trials (majority studying diabetic neuropathy with one chemotherapy induced peripheral neuropathy), and found that 'exercise is safe, feasible, and beneficial' (Streckmann, Zopf, et al., 2014). One pilot study not included in the systematic review used the McGill pain questionnaire and Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) to evaluate a ten-week home exercise program in breast cancer patients experiencing painful CIPN. Enrolment was extremely low (n=14) and adherence was worse with a 50% drop-out rate (total of n=6). While the participants pain and S-LANSS scores were reduced, adherence to exercise must improve for this treatment to be beneficial (Wonders et al., 2013). A long-term follow up study on peripheral neuropathy risk factors in breast cancer survivors found an association between women who reported exercise (at least 30 minutes on most days) with a lower risk (12%) of peripheral neuropathy (Mustafa Ali, Moeller, Rybicki, & Moore, 2017). A recent 6-week home based progressive resistance and walking program has demonstrated improvements in patient reported CIPN symptoms including symptoms of numbness/tingling and hotness/coldness compared to controls (Kleckner et al., 2018).

Physical therapy programs for cancer rehabilitation are becoming more common and educate on the importance of exercise specific to neuropathic pain and TIPN. These programs often include postural correction, generalized stretching, gait retraining, cardiac conditioning, and strengthening. Incorporated in this training are exercises aimed at improvements in balance, fine dexterity, reaction time, coordination, and

overall gross motor function following sensory deficits and motor weakness resulting from the peripheral neuropathies.

CONCLUSION

The pathophysiology of TIPN is complex and poorly understood. Several theories outline possible mechanisms of action, but few effective treatments exist. The same can be said for pain of neuropathic origin. Poorly understood mechanisms inciting and maintaining neuropathic pain are complicated, and successful management often requires a combination of physical therapy, pharmacological drugs, and psychological intervention to minimize symptoms. The general health benefits of exercise are well established. The past two decades of research on cancer and physical activity has positively correlated the recovery of treatment side effects including neuropathy (Cormie et al., 2018; Furmaniak et al., 2016; Mustafa Ali et al., 2017; Warburton et al., 2007). The evidence for the role of exercise in primary cancer prevention and secondary recurrence has been associated in epidemiological research and a few clinical trials, however, a causal mechanism has not been identified. Animal models of exercise and neuropathic pain demonstrate diminished allodynia and hyperalgesia as well as improved sensory nerve regeneration (Grace et al., 2016; Shen et al., 2013; Stagg et al., 2011). It is conceivable that exercise can assist in attenuating neuropathic pain in cancer patients, minimize neuropathic symptoms, and other known taxane side effects including fatigue, mental alertness, depression, general strength, endurance, and flexibility. The goal of future research is to identify the specifics of exercise intensity,

frequency, duration, and type to provide the most benefit for prevention and treatment of taxane induced peripheral neuropathy and neuropathic pain.

REFERENCES

Armada-da-Silva, P. A., Pereira, C., Amado, S., & Veloso, A. P. (2013). Role of physical exercise for improving posttraumatic nerve regeneration. *International review of neurobiology, 109*, 125-149. doi:10.1016/B978-0-12-420045-6.00006-7; 10.1016/B978-0-12-420045-6.00006-7

Barton, D. L., Wos, E. J., Qin, R., Mattar, B. I., Green, N. B., Lanier, K. S., . . . Loprinzi, C. L. (2011). A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer, 19*(6), 833-841. doi:10.1007/s00520-010-0911-0

Baumann, F. T., Bloch, W., Weissen, A., Brockhaus, M., Beulertz, J., Zimmer, P., . . . Zopf, E. M. (2013). Physical Activity in Breast Cancer Patients during Medical Treatment and in the Aftercare - a Review. *Breast care (Basel, Switzerland), 8*(5), 330-334. doi:10.1159/000356172 [doi]

Bennett, G. J., Liu, G. K., Xiao, W. H., Jin, H. W., & Siau, C. (2011). Terminal arbor degeneration--a novel lesion produced by the antineoplastic agent paclitaxel. *The European journal of neuroscience, 33*(9), 1667-1676. doi:10.1111/j.1460-9568.2011.07652.x [doi]

Blaney, J. M., Lowe-Strong, A., Rankin-Watt, J., Campbell, A., & Gracey, J. H. (2013). Cancer survivors' exercise barriers, facilitators and preferences in the context of fatigue, quality of life and physical activity participation: a questionnaire-survey. *Psychooncology, 22*(1), 186-194. doi:10.1002/pon.2072

Brewer, J. R., Morrison, G., Dolan, M. E., & Fleming, G. F. (2016). Chemotherapy-induced peripheral neuropathy: Current status and progress. *Gynecologic oncology, 140*(1), 176-183. doi:10.1016/j.ygyno.2015.11.011 [doi]

Cioroiu, C., & Weimer, L. H. (2017). Update on Chemotherapy-Induced Peripheral Neuropathy. *Current neurology and neuroscience reports, 17*(6), 47-017-0757-0757. doi:10.1007/s11910-017-0757-7 [doi]

Clifford, B. K., Mizrahi, D., Sandler, C. X., Barry, B. K., Simar, D., Wakefield, C. E., & Goldstein, D. (2018). Barriers and facilitators of exercise experienced by cancer survivors: a mixed methods systematic review. *Support Care Cancer, 26*(3), 685-700. doi:10.1007/s00520-017-3964-5

Cooper, M. A., Kluding, P. M., & Wright, D. E. (2016). Emerging Relationships between Exercise, Sensory Nerves, and Neuropathic Pain. *Frontiers in neuroscience, 10*, 372. doi:10.3389/fnins.2016.00372 [doi]

Cormie, P., Atkinson, M., Bucci, L., Cust, A., Eakin, E., Hayes, S., . . . Adams, D. (2018). Clinical Oncology Society of Australia position statement on exercise in cancer care. *Med J Aust*.

Courneya, K. S., McKenzie, D. C., Mackey, J. R., Gelmon, K., Reid, R. D., Friedenreich, C. M., . . . Segal, R. J. (2008). Moderators of the effects of exercise training in breast cancer patients receiving chemotherapy: a randomized controlled trial. *Cancer, 112*(8), 1845-1853. doi:10.1002/cncr.23379

Courneya, K. S., Segal, R. J., McKenzie, D. C., Dong, H., Gelmon, K., Friedenreich, C. M., . . . Mackey, J. R. (2014). Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. *Med Sci Sports Exerc, 46*(9), 1744-1751. doi:10.1249/mss.0000000000000297

Devoogdt, N., Van Kampen, M., Geraerts, I., Coremans, T., Fieuws, S., Lefevre, J., . . . Christiaens, M. R. (2010). Physical activity levels after treatment for breast cancer: one-year follow-up. *Breast cancer research and treatment, 123*(2), 417-425. doi:10.1007/s10549-010-0997-6 [doi]

Dobson, J. L., McMillan, J., & Li, L. (2014). Benefits of exercise intervention in reducing neuropathic pain. *Front Cell Neurosci, 8*, 102. doi:10.3389/fncel.2014.00102

Doyle, T., Chen, Z., Muscoli, C., Bryant, L., Esposito, E., Cuzzocrea, S., . . . Salvemini, D. (2012). Targeting the overproduction of peroxynitrite for the prevention and reversal of paclitaxel-induced neuropathic pain. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 32*(18), 6149-6160. doi:10.1523/JNEUROSCI.6343-11.2012 [doi]

Eckhoff, L., Feddersen, S., Knoop, A. S., Ewertz, M., & Bergmann, T. K. (2015). Docetaxel-induced neuropathy: a pharmacogenetic case-control study of 150 women with early-stage breast cancer. *Acta Oncologica (Stockholm, Sweden), 54*(4), 530-537. doi:10.3109/0284186X.2014.969846 [doi]

Fallon, M. T., Storey, D. J., Krishan, A., Weir, C. J., Mitchell, R., Fleetwood-Walker, S. M., . . . Colvin, L. A. (2015). Cancer treatment-related neuropathic pain: proof of concept study with menthol--a TRPM8 agonist. *Support Care Cancer, 23*(9), 2769-2777. doi:10.1007/s00520-015-2642-8

Fitzpatrick, F. A., & Wheeler, R. (2003). The immunopharmacology of paclitaxel (Taxol), docetaxel (Taxotere), and related agents. *International immunopharmacology, 3*(13-14), 1699-1714. doi:S1567576903002078 [pii]

Furmaniak, A. C., Menig, M., & Markes, M. H. (2016). Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev, 9*, Cd005001. doi:10.1002/14651858.CD005001.pub3

Gewandter, J. S., Mohile, S. G., Heckler, C. E., Ryan, J. L., Kirshner, J. J., Flynn, P. J., . . . Morrow, G. R. (2014). A phase III randomized, placebo-controlled study of topical amitriptyline and ketamine for chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study of 462 cancer survivors. *Support Care Cancer, 22*(7), 1807-1814. doi:10.1007/s00520-014-2158-7

Giardini, A. C., Dos Santos, F. M., da Silva, J. T., de Oliveira, M. E., Martins, D. O., & Chacur, M. (2017). Neural Mobilization Treatment Decreases Glial Cells and Brain-Derived Neurotrophic Factor Expression in the Central Nervous System in Rats with Neuropathic Pain Induced by CCI in Rats. *Pain research & management, 2017*, 7429761. doi:10.1155/2017/7429761 [doi]

Global Burden of Disease Cancer, C., Fitzmaurice, C., Allen, C., Barber, R. M., Barregard, L., Bhutta, Z. A., . . . Naghavi, M. (2017). Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA oncology, 3*(4), 524-548. doi:10.1001/jamaoncol.2016.5688 [doi]

Gornstein, E., & Schwarz, T. L. (2014). The paradox of paclitaxel neurotoxicity: Mechanisms and unanswered questions. *Neuropharmacology, 76 Pt A*, 175-183. doi:10.1016/j.neuropharm.2013.08.016; 10.1016/j.neuropharm.2013.08.016

Gornstein, E. L., & Schwarz, T. L. (2017). Neurotoxic mechanisms of paclitaxel are local to the distal axon and independent of transport defects. *Experimental neurology, 288*, 153-166. doi:S0014-4886(16)30400-9 [pii]

Grace, P. M., Fabisiak, T. J., Green-Fulgham, S. M., Anderson, N. D., Strand, K. A., Kwilasz, A. J., . . . Watkins, L. R. (2016). Prior voluntary wheel running attenuates neuropathic pain. *Pain, 157*(9), 2012-2023. doi:10.1097/j.pain.0000000000000607 [doi]

Grisold, W., Cavaletti, G., & Windebank, A. J. (2012). Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro-oncology, 14 Suppl 4*, iv45-54. doi:10.1093/neuonc/nos203; 10.1093/neuonc/nos203

Gutierrez-Gutierrez, G., Sereno, M., Miralles, A., Casado-Saenz, E., & Gutierrez-Rivas, E. (2010). Chemotherapy-induced peripheral neuropathy: clinical features, diagnosis, prevention and treatment strategies. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico, 12*(2), 81-91. doi:10.1007/S12094-010-0474-z; 10.1007/S12094-010-0474-z

Han, Y., & Smith, M. T. (2013). Pathobiology of cancer chemotherapy-induced peripheral neuropathy (CIPN). *Frontiers in pharmacology, 4*, 156. doi:10.3389/fphar.2013.00156 [doi]

Haroutounian, S., Nikolajsen, L., Bendtsen, T. F., Finnerup, N. B., Kristensen, A. D., Hasselstrom, J. B., & Jensen, T. S. (2014). Primary afferent input critical for maintaining spontaneous pain in peripheral neuropathy. *Pain, 155*(7), 1272-1279. doi:10.1016/j.pain.2014.03.022; 10.1016/j.pain.2014.03.022

Hayes, S. C., Johansson, K., Stout, N. L., Prosnitz, R., Armer, J. M., Gabram, S., & Schmitz, K. H. (2012). Upper-body morbidity after breast cancer: incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. *Cancer, 118*(8 Suppl), 2237-2249. doi:10.1002/cncr.27467; 10.1002/cncr.27467

Hershman, D. L., Lacchetti, C., Dworkin, R. H., Lavoie Smith, E. M., Bleeker, J., Cavaletti, G., . . . American Society of Clinical, O. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 32*(18), 1941-1967. doi:10.1200/JCO.2013.54.0914; 10.1200/JCO.2013.54.0914

Hershman, D. L., Unger, J. M., Crew, K. D., Minasian, L. M., Awad, D., Moinpour, C. M., . . . Albain, K. S. (2013). Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31*(20), 2627-2633. doi:10.1200/JCO.2012.44.8738; 10.1200/JCO.2012.44.8738

Hershman, D. L., Weimer, L. H., Wang, A., Kranwinkel, G., Brafman, L., Fuentes, D., . . . Crew, K. D. (2011). Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. *Breast cancer research and treatment, 125*(3), 767-774. doi:10.1007/s10549-010-1278-0; 10.1007/s10549-010-1278-0

Hoeijmakers, J. G., Faber, C. G., Lauria, G., Merkies, I. S., & Waxman, S. G. (2012). Small-fibre neuropathies--advances in diagnosis, pathophysiology and management. *Nature*

reviews.Neurology, 8(7), 369-379. doi:10.1038/nrneurol.2012.97; 10.1038/nrneurol.2012.97

Hong, J. S., Tian, J., & Wu, L. H. (2014). The influence of chemotherapy-induced neurotoxicity on psychological distress and sleep disturbance in cancer patients. *Current oncology (Toronto, Ont.), 21*(4), 174-180. doi:10.3747/co.21.1984 [doi]

Kandula, T., Farrar, M. A., Kiernan, M. C., Krishnan, A. V., Goldstein, D., Horvath, L., . . . Park, S. B. (2017). Neurophysiological and clinical outcomes in chemotherapy-induced neuropathy in cancer. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 128*(7), 1166-1175. doi:S1388-2457(17)30155-4 [pii]

Katzmarzyk, P. T., & Ardern, C. I. (2004). Overweight and obesity mortality trends in Canada, 1985-2000. *Canadian journal of public health = Revue canadienne de sante publique, 95*(1), 16-20.

Kerckhove, N., Collin, A., Conde, S., Chaleteix, C., Pezet, D., & Balayssac, D. (2017). Long-Term Effects, Pathophysiological Mechanisms, and Risk Factors of Chemotherapy-Induced Peripheral Neuropathies: A Comprehensive Literature Review. *Frontiers in pharmacology, 8*, 86. doi:10.3389/fphar.2017.00086 [doi]

Kleckner, I. R., Kamen, C., Gewandter, J. S., Mohile, N. A., Heckler, C. E., Culakova, E., . . . Mustian, K. M. (2018). Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. *Support Care Cancer, 26*(4), 1019-1028. doi:10.1007/s00520-017-4013-0

Knop, K., Schwan, R., Bongartz, M., Bloch, W., Brixius, K., & Baumann, F. (2011). Sport and oxidative stress in oncological patients. *International Journal of Sports Medicine, 32*(12), 960-964. doi:10.1055/s-0031-1283180 [doi]

Kus, T., Aktas, G., Kalender, M. E., Sevinc, A., Kul, S., Suner, A., . . . Camci, C. (2016). Taxane-induced peripheral sensorial neuropathy in cancer patients is associated with duration of diabetes mellitus: a single-center retrospective study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 24*(3), 1175-1179. doi:10.1007/s00520-015-2898-z [doi]

Lauria, G. (2005). Small fibre neuropathies. *Current opinion in neurology, 18*(5), 591-597.

Lundborg, G. (2000). Brain plasticity and hand surgery: an overview. *Journal of hand surgery (Edinburgh, Scotland), 25*(3), 242-252. doi:10.1054/jhsb.1999.0339

McTiernan, A. (2008). Mechanisms linking physical activity with cancer. *Nature reviews.Cancer, 8*(3), 205-211. doi:10.1038/nrc2325 [doi]

Miltenburg, N. C., & Boogerd, W. (2014). Chemotherapy-induced neuropathy: A comprehensive survey. *Cancer treatment reviews, 40*(7), 872-882. doi:10.1016/j.ctrv.2014.04.004 [doi]

Moulin, D., Boulanger, A., Clark, A. J., Clarke, H., Dao, T., Finley, G. A., . . . Williamson, O. D. (2014). Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain research & management : the journal of the Canadian Pain Society = journal de la societe canadienne pour le traitement de la douleur, 19*(6), 328-335.

Mustafa Ali, M., Moeller, M., Rybicki, L., & Moore, H. C. F. (2017). Long-term peripheral neuropathy symptoms in breast cancer survivors. *Breast cancer research and treatment*. doi:10.1007/s10549-017-4437-8 [doi]

Park, J. S., Kim, S., & Hoke, A. (2015). An exercise regimen prevents development paclitaxel induced peripheral neuropathy in a mouse model. *Journal of the peripheral nervous system : JPNS, 20*(1), 7-14. doi:10.1111/jns.12109 [doi]

Park, S. B., Lin, C. S., Krishnan, A. V., Friedlander, M. L., Lewis, C. R., & Kiernan, M. C. (2011). Early, progressive, and sustained dysfunction of sensory axons underlies paclitaxel-induced neuropathy. *Muscle & nerve, 43*(3), 367-374. doi:10.1002/mus.21874; 10.1002/mus.21874

Pike, C. T., Birnbaum, H. G., Muehlenbein, C. E., Pohl, G. M., & Natale, R. B. (2012). Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and nonsmall cell lung cancer. *Chemotherapy research and practice, 2012*, 913848. doi:10.1155/2012/913848 [doi]

Poupon, L., Kerckhove, N., Vein, J., Lamoine, S., Authier, N., Busserolles, J., & Balayssac, D. (2015). Minimizing chemotherapy-induced peripheral neuropathy: preclinical and clinical development of new perspectives. *Expert opinion on drug safety, 14*(8), 1269-1282. doi:10.1517/14740338.2015.1056777 [doi]

Rogers, L. Q., Courneya, K. S., Verhulst, S., Markwell, S. J., & McAuley, E. (2008). Factors associated with exercise counseling and program preferences among breast cancer survivors. *J Phys Act Health, 5*(5), 688-705.

Rosen, B., Bjorkman, A., & Lundborg, G. (2006). Improved sensory relearning after nerve repair induced by selective temporary anaesthesia - a new concept in hand rehabilitation. *Journal of hand surgery (Edinburgh, Scotland), 31*(2), 126-132. doi:10.1016/j.jhsb.2005.10.017

Seretny, M., Currie, G. L., Sena, E. S., Ramnarine, S., Grant, R., MacLeod, M. R., . . . Fallon, M. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain, 155*(12), 2461-2470. doi:10.1016/j.pain.2014.09.020; 10.1016/j.pain.2014.09.020

Shen, J., Fox, L. E., & Cheng, J. (2013). Swim therapy reduces mechanical allodynia and thermal hyperalgesia induced by chronic constriction nerve injury in rats. *Pain medicine (Malden, Mass.), 14*(4), 516-525. doi:10.1111/pme.12057 [doi]

Sisignano, M., Baron, R., Scholich, K., & Geisslinger, G. (2014). Mechanism-based treatment for chemotherapy-induced peripheral neuropathic pain. *Nature reviews.Neurology, 10*(12), 694-707. doi:10.1038/nrneurol.2014.211 [doi]

Smith, E. M., Pang, H., Cirrincione, C., Fleishman, S., Paskett, E. D., Ahles, T., . . . Alliance for Clinical Trials in, O. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *Jama, 309*(13), 1359-1367. doi:10.1001/jama.2013.2813 [doi]

Speck, R. M., Sammel, M. D., Farrar, J. T., Hennessy, S., Mao, J. J., Stineman, M. G., & DeMichele, A. (2013). Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in nonmetastatic breast cancer. *Journal of oncology practice / American Society of Clinical Oncology, 9*(5), e234-240. doi:10.1200/JOP.2012.000863; 10.1200/JOP.2012.000863

Stagg, N. J., Mata, H. P., Ibrahim, M. M., Henriksen, E. J., Porreca, F., Vanderah, T. W., & Philip Malan, T., Jr. (2011). Regular exercise reverses sensory hypersensitivity in a rat

neuropathic pain model: role of endogenous opioids. *Anesthesiology, 114*(4), 940-948. doi:10.1097/ALN.0b013e318210f880 [doi]

Starobova, H., & Vetter, I. (2017). Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. *Frontiers in molecular neuroscience, 10*, 174. doi:10.3389/fnmol.2017.00174 [doi]

Streckmann, F., Kneis, S., Leifert, J. A., Baumann, F. T., Kleber, M., Ihorst, G., . . . Bertz, H. (2014). Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Annals of oncology : official journal of the European Society for Medical Oncology, 25*(2), 493-499. doi:10.1093/annonc/mdt568 [doi]

Streckmann, F., Zopf, E. M., Lehmann, H. C., May, K., Rizza, J., Zimmer, P., . . . Baumann, F. T. (2014). Exercise intervention studies in patients with peripheral neuropathy: a systematic review. *Sports medicine (Auckland, N.Z.), 44*(9), 1289-1304. doi:10.1007/s40279-014-0207-5 [doi]

Visovsky, C., Collins, M., Abbott, L., Aschenbrenner, J., & Hart, C. (2007). Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. *Clinical journal of oncology nursing, 11*(6), 901-913. doi:10.1188/07.CJON.901-913

Warburton, D. E., Katzmarzyk, P. T., Rhodes, R. E., & Shephard, R. J. (2007). Evidence-informed physical activity guidelines for Canadian adults. *Canadian journal of public health = Revue canadienne de sante publique, 98 Suppl 2*, S16-68.

Wing, C., Komatsu, M., Delaney, S. M., Krause, M., Wheeler, H. E., & Dolan, M. E. (2017). Application of stem cell derived neuronal cells to evaluate neurotoxic chemotherapy. *Stem cell research, 22*, 79-88. doi:S1873-5061(17)30106-X [pii]

Wonders, K. Y., Whisler, G., Loy, H., Holt, B., Bohachek, K., & Wise, R. (2013). Ten Weeks of Home-Based Exercise Attenuates Symptoms of Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer Patients. *Health psychology research, 1*(3), e28. doi:10.4081/hpr.2013.e28 [doi]

Xiao, W. H., Zheng, H., & Bennett, G. J. (2012). Characterization of oxaliplatin-induced chronic painful peripheral neuropathy in the rat and comparison with the neuropathy induced by paclitaxel. *Neuroscience, 203*, 194-206. doi:10.1016/j.neuroscience.2011.12.023 [doi]

Yarnitsky, D., Crispel, Y., Eisenberg, E., Granovsky, Y., Ben-Nun, A., Sprecher, E., . . . Granot, M. (2008). Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain, 138*(1), 22-28. doi:10.1016/j.pain.2007.10.033

Zimmer, P., Bloch, W., Schenk, A., Zopf, E. M., Hildebrandt, U., Streckmann, F., . . . Baumann, F. (2015). Exercise-induced Natural Killer Cell Activation is Driven by Epigenetic Modifications. *International Journal of Sports Medicine, 36*(6), 510-515. doi:10.1055/s-0034-1398531 [doi]

CHAPTER 3: Physical Therapy and Nerve Gliding Exercises for the Treatment of Chemotherapy Induced Peripheral Neuropathy

Running Head: Physical Therapy for the Treatment of CIPN

MY CONTRIBUTION TO THE MANUSCRIPT

The development of the of physical therapy paper was a joint collaboration between Dr. Barbara Shay, Dr. Marshall Pitz and myself. I completed the literature search, developed the research questions and protocol with guidance, assisted in grant writing, completed ethics applications to both the Health Research Ethics Board and Research Resource Impact Committee. Dr. Pitz, Linda Davidson, and Lori Santoro were vital to recruitment by informing patients of the trial and signing consent to contact forms. I completed recruitment, consented and assessed participants throughout the duration of chemotherapy to the final appointment 6 months post-chemotherapy. Karen Steinfeld developed the home program and administered the 3 physical therapy treatment sessions. I ran the project for the 3 years of data collection. Pascal Lambert analyzed the data. I interpreted the results and prepared the manuscript for publication in a peer reviewed journal.

ABSTRACT

Purpose: To evaluate the role of a physical therapy nerve gliding home program during chemotherapy for the prevention and management of chemotherapy induced peripheral neuropathy (CIPN) and evaluate whether a dual nerve disorder exists between the surgical and non-surgical side using quantitative sensory testing (QST).

Methods: Single blind (blinded assessor) randomized controlled pilot study compared standard care to a nerve specific physical therapy home program throughout chemotherapy. Patient questionnaires and QST were used to evaluate the treatment effect of these exercises for the hands on 4 reassessment visits (1) midway through chemotherapy, 2) post chemotherapy, 3) 3 months post chemotherapy and 4) 6 months post chemotherapy). QST further identified whether sensory impairments were present between surgical and non-surgical side. Treatment consisted of three appointments with a physical therapist to develop an upper extremity nerve gliding home program. The control group received standard care.

Results: Stage I-III patients with breast cancer (n=48) were included in analysis. The 11-point numeric pain rating scale (NPRS) was converted to percentages of participants with no pain (0/10) or 1/10 and higher. 30% of participants in the treatment group had pain scores >1 compared to 49% in the control group. Using logistic mixed models for binary outcomes the treatment group had less pain (OR 0.41, 95% confidence 0.17-1.01; p=0.053) and pain decreased over time (OR 0.85, 95% CI 0.76-0.94; p=0.002). Using Linear mixed models predicted for continuous outcomes, pain pressure thresholds (p=0.03) and grip dynamometry (p>0.0001) were improved in the treatment

group. Inconsistent results between left and right surgical side countered the hypothesis that sensory differences would be evident between the surgical and non-surgical side. Conclusion: Physical therapy and nerve gliding home exercises during and after chemotherapy improves CIPN pain and function in the upper extremity for patients with breast cancer. Surgical tumor excision prior to chemotherapy was not found to be a contributing risk factor for severity of CIPN symptoms on the surgical side.

KEY WORDS: chemotherapy induced peripheral neuropathy (CIPN), physical therapy, nerve gliding, neural gliding, nerve mobilizations, dual nerve disorder

INTRODUCTION

Taxanes (Docetaxel or Paclitaxel) are widely used chemotherapeutic agents for the treatment of many solid tumors that prevent tumor growth through microtubule stabilizing mechanisms. A common side effect is chemotherapy induced peripheral neuropathy (CIPN). CIPN is a small fibre sensory neuropathy that develops in the hands/feet and worsens with increasing dose and duration of treatment. It impacts the Aβ, Aδ, and C-Fiber function involved in light touch and vibration sense, thermal detection and thermal pain. This results in a variety of positive and/or negative sensory symptoms including hypoesthesia, dysesthesias, hyperalgesia, allodynia and neuropathic pain. The majority of patients receiving taxane chemotherapy experience CIPN, 60% will continue to have symptoms months after chemotherapy is complete, and 25% will have severe sensory disturbances for years post-treatment (Hershman et al., 2011; Park et al., 2011). CIPN symptom severity has been reported to cause dose reduction or treatment delay in 10% of individuals (Seretny et al., 2014). At present, there are few effective treatment options for chemotherapy induced peripheral neuropathy. Moderate support for the serotonin norepinephrine re-uptake inhibitor, Duloxetine, has been shown to improve pain associated with CIPN sensory symptoms, however, common side effects including nausea, dry mouth, fatigue, dizziness, sweating and constipation limit use (Moulin et al., 2014; Smith et al., 2013). Expert opinion from the Canadian pain society recommends physical therapy and psychological treatment in conjunction with pharmacological agents to optimize success (Moulin et al., 2014).

Risk factors that have been identified include advanced age, previous chemotherapy, exposure to toxins, and genetic disorders known to cause peripheral neuropathic symptoms. These factors can predispose the patient to more severe symptoms of the neuropathy (Grisold, Cavaletti, & Windebank, 2012). One potential risk factor that has been mentioned, but not studied, is pre-existing nerve health (Stubblefield, McNeely, Alfano, & Mayer, 2012). Mechanical entrapment neuropathies (such as carpal tunnel syndrome) and decreased neural excursion on nerve testing (such as post-operative nerve irritation/compression from breast surgery) may sensitize the nerve to further injury with the chemotherapy drug. 'An axon damaged at one site can become more vulnerable to further trauma at a secondary site along the length of the nerve' and is termed the double crush injury or dual nerve disorder (Upton & McComas, 1973). A recent Delphi review on dual nerve disorders discussed the possibility that a nerve injury combined with neurotoxic medication would likely compound the effects (Schmid, Nee, & Coppieters, 2013). Physical therapy treatment for nerve disorders is well established in orthopedics and plastic surgery for entrapment neuropathies, neuropathic pain, post-operative nerve repair and regeneration (Armada-da-Silva, Pereira, Amado, & Veloso, 2013; Butler, 2000; Hunt, 2002; Novak & von der Heyde, 2013; Schmid et al., 2009; Schmid, Elliott, Strudwick, Little, & Coppieters, 2012). If pre-existing nerve health is an additional risk factor, it is possible that physiotherapy intervention prior to or during chemotherapy could improve the chances of full nerve recovery post-chemotherapy. This would potentially greatly improve quality of life for many cancer survivors reducing the burden of disease.

The purpose of the present study was to evaluate the role for an upper extremity nerve mobilization home physical therapy program during chemotherapy for the prevention and management of CIPN and evaluate whether a dual nerve disorder contributes to severity of symptoms. Patient questionnaires and quantitative sensory testing (QST) were used to evaluate the treatment effect of these exercises.

Hypothesis

1) Physical therapy and nerve gliding exercises would assist patients with breast cancer in managing upper extremity CIPN symptoms during chemotherapy and report improved pain (NPRS) and function (DASH) compared to the control group. Secondary outcome measures included vibration, pain pressure and grip strength. It was hypothesized that the treatment group would have improved pain, grip and vibration sense compared to controls.
2) Participants with a prior history of nerve damage will demonstrate greater impairment on the affected side. Additionally, the surgical side will demonstrate greater impaired sensory function on QST testing compared to the non-surgical side further supporting the dual nerve disorder hypothesis

METHODS

Participants and eligibility

Stage I-III patients with breast cancer that attended oncology clinics at CancerCare Manitoba were eligible for enrolment if they were receiving standard taxane chemotherapy. Two different chemotherapy regimens were included 1) docetaxel

75mg/m2 and cyclophosphamide x 4 (TC) or 2) 5-fluorouracil, epirubicin, cyclophosphamide x3, followed by Docetaxel 100mg/m2 x 3 (FECD)(Jones et al., 2009; Roche et al., 2006; Swain et al., 2013). Participants were approached by a member of the team at their initial oncology visit to advise them of the physical therapy study taking place. If interested, patients signed a consent to contact form. Participants were excluded if they had co-morbid conditions causing peripheral neuropathic symptoms (including previous chemotherapy) or patients not scheduled for regular Taxane therapy. In total, 80 patients were contacted to participate between November 2014 and January 2017. Sixty-one participants were enrolled and 7 withdrew over the course of the study. Reasons for withdrawal included too ill to continue, too busy to continue, or re-diagnosed as stage IV. Data collection was complete by October of 2017 and consisted of 54 participants. Six participants had received neo-adjuvant chemotherapy or chemotherapy that differed from the TC or FECD regimes and were excluded from analysis because these regimes substantially affected the timing for surgery, and in some cases, the overall dose of taxane chemotherapy. Forty-eight participants were then included for analysis. Figure 1. Provides a consort diagram of the enrolment process.

Protocol

This was a single blind (blinded assessor) randomized controlled pilot study testing the potential for nerve specific home exercises to improve pain and function post-surgery during and after chemotherapy. Random numbers were drawn to assign either treatment or control. Envelopes containing the assigned group were sealed and

the blinded assessor needed only to provide the envelope to the participant after initial consent and assessment. Ethics approval was obtained from both the Health Research Ethics Board (H:2014:281) at the University of Manitoba and the Research Resource Impact Committee (RRIC 2014-031) at CancerCare Manitoba.

Nerve assessments using quantitative sensory testing were administered at the Pain Research Laboratory (PRL), College of Rehabilitation Sciences, University of Manitoba. Quantitative sensory testing (QST) are a variety of non-invasive tests aimed at quantifying sensory perceptions commonly used in research (Boyette-Davis et al., 2013; Hershman et al., 2011; Park et al., 2011; Walk et al., 2009). It is used for sensory detection and pain thresholds for both mechanical and thermal stimuli. The advantages of using QST are that, 'the experimental stimulus, intensity, duration, and modality are controlled; the responses are quantifiable; and, can be compared over time' (Arendt-Nielsen & Yarnitsky, 2009).

Outcome Measures

Primary Outcome Measures for Physical Therapy Intervention

The primary outcome measures related to function and quality of life and included the Numeric Pain Rating Scale (NPRS), the Disability of the Arm, Shoulder and Hand (DASH), and the Self report version of the Leeds Assessment for Neuropathic Symptoms and Signs (S-LANSS).

1) Numeric Pain Rating Scale (NPRS) rated CIPN pain. The NPRS is an 11 point scale (0-10) ranking pain from 0 indicating no pain at all to 10 indicating worst pain imaginable

on each assessment visit of the finger tips. This was to specifically identify pain from CIPN. A change score of 2 is reported to be a clinically relevant change.

2) Disability of the Arm, Shoulder and Hand (DASH) is a 30 item participant reported questionnaire commonly used to gauge upper limb function (attached in appendix E). The DASH was chosen because of high test-retest reliability and the responsiveness and construct validity in patients with breast cancer over other quality of life measures (Beaton et al., 2001; Harrington, Michener, Kendig, Miale, & George, 2014). A minimal clinical important difference is a change score of 15.

3) Self report version of Leeds Assessment for Neuropathic Symptoms and Signs (S-LANSS) is a 7 item patient reported questionnaire and was used to confirm the presence of neuropathic pain (Bennett, Smith, Torrance, & Potter, 2005). The score ranges from 0-19 with a score above 12 indicative of neuropathic pain/symptoms. S-LANSS was chosen because of its' specificity and accuracy in a cancer population (Hardy, Quinn, Fazekas, Agar, & Currow, 2013; Perez et al., 2015). Participants were requested to answer specifically for the hands, not feet (attached in appendix E).

<u>Secondary Outcome Measures for Physical Therapy Intervention</u>

Secondary outcomes included vibration sensation assessment as a measure of Aβ function, pain pressure thresholds as a measure of central sensitization, and grip strength as a general measure of function.

1) Vibration analysis testing for perception thresholds are specific to Aβ nerve fibres. The TSAII Vibration Sensory Analyzer module for the Medoc was used. The pulp of the

index finger lightly touches the sensor. The sensor delivers different vibration amplitudes (µm). Random, varying vibration thresholds are delivered with the participant responding “yes/no” to sensing the vibration. Vibration perception was selected for its sensitivity and has been suggested to be the first clinical sign of CIPN symptoms and was tested bilaterally (Gutierrez-Gutierrez, Sereno, Miralles, Casado-Saenz, & Gutierrez-Rivas, 2010).

2) Pressure Algometry measured pressure/pain thresholds. It is a hand-held device (Somedic AB, Sweden) and applied perpendicular to the muscles being tested. Increasing pressure is applied until the participant determines that the sensation has changed from a feeling of pressure to a feeling of pain. The test stops when the participant presses a button, and the force (Kpa) was recorded. The left quadriceps muscle was tested as a measure of central sensitization.

3) Hand Dynamometry records grip strength in kgs and was used as a measure of function (3 trials). The dominant hand was tested. For our participants, all 48 in analysis were right handed.

Outcome Measures Assessing Dual Nerve Disorder

QST using the neurosensory analyzer (TSA II, Medoc) for thermal and vibration sensation quantified the differences between surgical and non-surgical side.

1) Thermal detection threshold (warm and cool) and thermal pain thresholds (hot and cold) measured Aδ and C-fibre function. The Neurosensory Analyzer (TSA ll, Medoc, Israel) thermode was attached to the volar surface of the index and middle distal

phalanx. Temperature was increased or decreased by 0.1-degree Celsius increments until the patient pressed a button indicating temperature detection or thermal pain. The patient is always in control and is never at risk for tissue damage (temperature limits are set to vary only from 0-50 degrees Celsius). Hands were tested bilaterally.

2) Vibration analysis testing from the physical therapy data was used for Aβ nerve fibre function (Vibration Sensory Analyzer module, TSA II).

3) Volumeter assessment as a gross measure of hand swelling. The volumeter objectively records changes in swelling over time. The hand is submerged in water to a set point where the web space of the middle and ring finger touch a bar in the centre of the container. The volume of water displaced into an overflow container is used as a measure of swelling to compare within subject variability over time.

Assessment Visits

Five visits in total with the research coordinator were required over an average of 8 months at the Pain Research Laboratory (PRL), College of Rehabilitation Sciences, University of Manitoba. The first visit proceeded after the initial oncology visit confirmed chemotherapy was required. This primary assessment (visit 1) consisted of completing the informed consent and baseline nerve evaluation including the subjective questionnaires and QST data. Pre-randomized envelopes were sent home with participants that contained which experimental group they were assigned to either physical therapy treatment or standard care. Participants were advised not to disclose

their assigned group to the research coordinator in order to maintain blinding. If participants had questions, they were to contact the oncologist or co-investigator involved in the study. Standard care for the control group was to attend nerve re-assessments at the pain research laboratory, but no exercises or appointments with a physical therapist were provided. Instructions only in the treatment group envelope directed participants to arrange 3 sessions at their convenience with the physical therapist prior to the start of chemotherapy.

An estimated nerve re-assessment date for Visit 2 was scheduled for all participants based on their treatment cycles and start date. Visit 3 was post-chemotherapy. Visit 4 was 3 months post-chemotherapy and Visit 5 was the final assessment at 6 months post-chemotherapy. After final evaluation participants could disclose whether they were treatment or control, and they signed a form to receive a $70 honorarium to cover transportation costs. Patients with residual symptoms allocated to the control group were then offered a physical therapy assessment and tailored home program.

Physical Therapy treatment

Three visits with a certified hand physical therapist to develop a home exercise and education program were provided to each of the participants in the treatment group prior to their first round of chemotherapy. The three appointments provided upper extremity nerve gliding exercises that were the focus of the daily home program and upper extremity range of motion exercises to restore pre-operative range, if required. Nerve gliding exercises are frequently used exercises to improve neural excursion

across joints, improve pain and decrease inflammation (Coppieters & Butler, 2008; Nee, Vicenzino, Jull, Cleland, & Coppieters, 2012; Schmid et al., 2012). Nerve gliding exercises were completed several times daily and required approximately 5-10 minutes of time to complete. Participants were advised to complete these exercises during chemotherapy and after until the symptoms of neuropathy subsided.

Education was provided on how to manage symptoms of neuropathic pain, cold intolerance and hyperalgesia. This included the possibility of using compression gloves, heated mittens, resting splints and desensitization exercises. Education was also provided for hypoesthesia symptoms including safety and protection. Stretching exercises for the neck and upper limb and axillary webbing exercises were provided if appropriate. All the information was contained in an education package. Only one follow up phone call, 6 weeks after the last treatment appointment, was provided by the physical therapist. The purpose of the call was to ask if they had questions about the exercises and encourage compliance. Therefore, both the treatment and control group received no active intervention during or after chemotherapy in order to avoid a possible treatment effect.

Data Analysis

Outcomes for the effect of the treatment and control groups were analyzed with a mixed models analysis, which can account for repeated measurements, unequal time intervals and data missing at random. Comparisons were made during follow up. One mid-chemotherapy re-assessment time point was missing from analysis as the participant was too sick to attend. Linear mixed models were used to predict continuous

outcomes when the assumption of normality was met. Quantile mixed models were used to predict ordinal outcomes or continuous outcomes where the assumption of normality was not met. More than half of the NPRS pain scores were 0 indicating 'no pain'. Due to the floor effect of the pain scores, the scale was dichotomized into 0 and 1+ for analysis. Logistic mixed models were used for predicting binary outcomes, and the results were marginalized using the approach by Hedeker et al. (Hedeker, Toit, Demirtas, & Gibbons, 2018) that converts the 'subject-specific' estimates to 'population-averaged' estimates. Residual plots were used to evaluate the assumption of normality and to detect outliers. The assumption of linearity for continuous predictors was evaluated using restricted cubic splines. The predictors for the odds ratio were treatment variable and follow up time. Analyses were run using the R project for statistical computing software version 3.4.1. (R Development team, 2017) and SAS 9.4.

RESULTS

Demographics

Forty-eight stage I-III breast cancer participants scheduled to receive adjuvant chemotherapy were followed post-surgery until 6 months post-chemotherapy. Participants were followed for an average of 8.25 months (range 6.6-9.4 months). One mid-chemotherapy visit was missed in the treatment group as the participant was too sick to attend. This left 87 reassessment visits in the treatment group (n=22) and 104 in the control group (n=26). The mean age was 61.5 years (range 37-78). There were no statistical differences between the groups. Demographics in Table 1. shows age, stage,

surgery, reconstruction, radiation treatment, cancer side, and chemotherapy regimen for all treatment and control participants.

Physical Therapy Intervention

On analysis, the distribution of NPRS scores prevented the use of the 11 point scale for interpretation. Instead, the NPRS was reported as percentages of those having no pain versus pain to interpret the data using logistic mixed models predicting binary outcomes. Pain was defined as an NPRS of 1 or more (1+) on the 11-point scale. 30% of participants in the treatment group had 1+ pain scores compared to 49% in the control group. Predicting 1+ pain for NPRS demonstrated that the treatment group had less pain (OR 0.41, 95% CI 0.17-1.01; p=0.05). This represents comparison between the groups at all assessment time points while controlling for the effect of time. The NPRS treatment group also demonstrated a significant decrease in pain over time (OR 0.85, 95% CI 0.76-0.94; p=0.002). Using Linear mixed models predicted for continuous outcomes, pain pressure thresholds (p=0.03) and grip dynamometry (p<0.0001) were improved in the treatment group. Linear mixed models for both pain pressure and grip strength demonstrated non-significant changes over time. No statistically significant outcomes were found for the DASH, S-LANSS and vibration sensation. Figure 2 provides results for the NPRS. Figure 3 provides results for pain pressure algometry. Figure 4 provides results for grip dynamometry. Table 2. Physical Therapy Intervention summarizes all the findings for both the quantitative sensory data and subjective questionnaires for the treatment and control participants.

Dual Nerve Disorder

Surgical side compared to non-surgical side was used to assess whether a dual nerve disorder was evident from tumor excision surgery combined with chemotherapy. Using linear mixed models, the results demonstrated statistically significant increase in volume for right sided surgery (mean 6.47, 95%CI 2.13-10.81; p=0.004) while left sided surgery had a decrease in volume (mean -7.16, 95%CI -11.48 - -2.88; p=0.001). Vibration demonstrated statistically significant improvement for left sided surgery (mean -0.09, 95%CI -0.18 - -0.01; p=0.04) but not right sided surgery (NS). Cool detection thresholds were impaired for left sided surgery (mean 0.47, 95%CI 0.02-0.91; p=0.04) but improved for right sided surgery (mean -0.51 95%CI -0.89 - -0.13; p=0.01). Warm detection demonstrated improvement for left sided surgery (mean -0.71 95%CI -1.30 - -0.13; p=0.02) but not right sided surgery (NS). No differences were observed for either hot or cold pain thresholds.

DISCUSSION

To our knowledge, this is the first study to use physical therapy and nerve gliding home exercises in an attempt to minimize the effects of CIPN. The physical therapy treatment group reported statistically significant improvements for CIPN pain on the NPRS, improved pain pressure thresholds (as a measure of centralized pain), and improved grip strength (general upper extremity function measure) compared to the control group.

A study by Kelley and Jull in 1998 was the first to show sensitivity during movement in the neural tissue following breast cancer surgery. The authors used an

upper limb tension test (ULTT2a) which is a specific test for brachial plexus mobility with emphasis on the median nerve pre and post-operatively. The results demonstrated as expected, a reduction in ipsilateral shoulder abduction post-surgery compared to pre-surgery. Less expected was a post-operative bilateral decrease of shoulder abduction. The authors attribute the bilateral limitations in range of motion to the presence of centrally controlled protective muscle spasms from the local neural irritation (Kelley & Jull, 1998). Another study replicated these findings despite having a more heterogeneous population that included participants with lymphedema and a variable time to post-operative assessment visits (Smoot, Boyd, Byl, & Dodd, 2014). Taken together, the results from both studies demonstrate that neural tissue sensitivity is a common symptom for many women post-surgery, and that symptoms extend past the usual post-operative wound healing phase.

Sensitized neural tissues pre-chemotherapy may well pre-dispose the nerves to further trauma from chemotherapy and/or radiation resulting in a double-crush syndrome or dual nerve disorder prolonging symptoms. Our study selected nerve gliding exercises aiming to normalize nerve excursion, decrease pain and sensitivity, and prevent loss of ROM from post-operative scarring prior to chemotherapy. Our results along with others support the use of physical therapy to minimize upper extremity morbidity (Hayes et al., 2012; Stubblefield et al., 2012). Additionally, there may be a role for nerve specific exercises throughout chemotherapy to minimize pain and help restore function for breast cancer survivors. Our results are similar to the results of a nerve gliding program for neck and arm pain. Four sessions of a nerve

gliding program provided clinically important changes in neck and arm pain as well as self-report functional measures (Nee et al., 2012).

Physical therapy treatment for nerve disorders is well established for entrapment, neuropathic pain, nerve repair and regeneration (Armada-da-Silva et al., 2013; Butler, 2000; Hunt, 2002; Novak & von der Heyde, 2013; Schmid et al., 2009; Schmid et al., 2012). Treatment addresses both positive and negative sensory symptoms that are involved in nerve compression injuries, crush injuries and nerve lacerations to improve pain and function, regain diminished sensation, and normalize hypersensitivity/allodynia (Novak & von der Heyde, 2013). Conservative treatment with physical therapy includes nerve gliding exercises that have been shown to reduce neural edema and decrease pressure in the carpal tunnel (Schmid et al., 2012) and restore function and improve pain in the neck and arm (Nee et al., 2012). Splinting is used to hold a joint in a position that maintains the least amount of pressure on the nerve and decrease edema. Compression garments are used to both to reduce edema and diminish positive sensory signs such as hyperalgesia and allodynia. Adaptive equipment can be prescribed to improve function with activities of daily life. Finally, physical therapy treatment provides pain management to restore function and diminish symptoms including both peripheral and central mechanisms. Centrally, physical therapy aims to restore cortical changes to the somatosensory cortical map that occur rapidly after sensory nerve injury (Lundborg, 2000; Novak & von der Heyde, 2013).

For the dual nerve disorder hypothesis, it was expected that the surgical side would consistently exhibit impairments in QST regardless of whether surgery was right sided or left sided. The results found no consistent pattern present on the

surgical/cancer side compared to the opposite limb. According to previous research 60% of women demonstrated decreased neural excursion post-operatively (Kelley & Jull, 1998). From this, it was hypothesized that impaired thermal and vibration sense would result. In light of the current findings, it was suspected that perhaps handedness may play a role. Of note, all 48 participants were right handed in the current trial. This contradicts our hypothesis that post-operative neural irritation is a risk factor for severity of CIPN symptoms. Too few participants had a history of either prior nerve damage or entrapment to allow for analysis based on previous history of nerve damage.

Limitations

Since we collected multiple outcome measures, it is possible that some variables deemed significant may be due to a random effect. However, the unilateral direction of improvements for all the quality of life variables in the physical therapy intervention group (NPRS, DASH, S-LANSS, functional grip strength) is reassuring. Quantitative sensory testing provides an objective stimulus but relies on a subjective patient response. Attention, focus and standardized instructions can all impact the response time and results. While great care was taken to ensure standard wording and testing procedures, participants focus and attention may have impacted the results. To verify the claims that all participants were completing their home program we requested that the treatment group keep an exercise diary. While all but two participants reported daily nerve gliding, only three participants completed the written diary. Recall from memory is not an accurate representation and future studies should have a way to confirm exercise adherence. Future studies should use the visual analog scale as a continuous

measure, instead of the NPRS to improve sensitivity. Finally, we chose to focus only on the hands even though CIPN is defined as a bilateral symmetric polyneuropathy affecting both the hands and feet. This was for two reasons. First, patients with breast cancer may benefit most from the range of motion and nerve exercises in the upper limb. The aim was to minimize a dual nerve disorder that may occur from chemotherapy and post-operative neural irritation. The addition of another package of exercises for the feet during treatment was thought to be too onerous, potentially reducing compliance. Second, QST and questionnaire assessments for both the hands and feet bilaterally would be too time consuming for participants that are unwell. We felt that attempting to assess all extremities may result in a larger attrition rate.

CONCLUSION

To our knowledge, no study to date has used physical therapy nerve gliding exercises to potentially manage or minimize neuropathy symptoms throughout chemotherapy. This study helps support a role for physical therapy post-operatively and throughout chemotherapy in improving quality of life for patients with breast cancer. A neural gliding and range of motion home program assists in improving pain during chemotherapy. Further research is needed to evaluate whether nerve gliding exercises can also minimize dose reductions or treatment delay for the improvement of chemotherapy treatment delivery.

REFERENCES

Arendt-Nielsen, L., & Yarnitsky, D. (2009). Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *The journal of pain : official journal of the American Pain Society, 10*(6), 556-572. doi:10.1016/j.jpain.2009.02.002; 10.1016/j.jpain.2009.02.002

Armada-da-Silva, P. A., Pereira, C., Amado, S., & Veloso, A. P. (2013). Role of physical exercise for improving posttraumatic nerve regeneration. *International review of neurobiology, 109*, 125-149. doi:10.1016/B978-0-12-420045-6.00006-7; 10.1016/B978-0-12-420045-6.00006-7

Beaton, D. E., Katz, J. N., Fossel, A. H., Wright, J. G., Tarasuk, V., & Bombardier, C. (2001). Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. *Journal of hand therapy : official journal of the American Society of Hand Therapists, 14*(2), 128-146.

Bennett, M. I., Smith, B. H., Torrance, N., & Potter, J. (2005). The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *The journal of pain : official journal of the American Pain Society, 6*(3), 149-158. doi:10.1016/j.jpain.2004.11.007

Boyette-Davis, J. A., Cata, J. P., Driver, L. C., Novy, D. M., Bruel, B. M., Mooring, D. L., . . . Dougherty, P. M. (2013). Persistent chemoneuropathy in patients receiving the plant alkaloids paclitaxel and vincristine. *Cancer chemotherapy and pharmacology, 71*(3), 619-626. doi:10.1007/s00280-012-2047-z; 10.1007/s00280-012-2047-z

Butler, D. (2000). *The Sensitive Nervous System*. Adelaide, Australia: NOI Group publications.

Coppieters, M. W., & Butler, D. S. (2008). Do 'sliders' slide and 'tensioners' tension? An analysis of neurodynamic techniques and considerations regarding their application. *Manual therapy, 13*(3), 213-221. doi:10.1016/j.math.2006.12.008

Grisold, W., Cavaletti, G., & Windebank, A. J. (2012). Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro-oncology, 14 Suppl 4*, iv45-54. doi:10.1093/neuonc/nos203; 10.1093/neuonc/nos203

Gutierrez-Gutierrez, G., Sereno, M., Miralles, A., Casado-Saenz, E., & Gutierrez-Rivas, E. (2010). Chemotherapy-induced peripheral neuropathy: clinical features, diagnosis, prevention and treatment strategies. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico, 12*(2), 81-91. doi:10.1007/S12094-010-0474-z; 10.1007/S12094-010-0474-z

Hardy, J., Quinn, S., Fazekas, B., Agar, M., & Currow, D. (2013). Can the LANSS scale be used to classify pain in chronic cancer pain trials? *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 21*(12), 3387-3391. doi:10.1007/s00520-013-1921-5 [doi]

Harrington, S., Michener, L. A., Kendig, T., Miale, S., & George, S. Z. (2014). Patient-reported upper extremity outcome measures used in breast cancer survivors: a systematic review. *Archives of Physical Medicine and Rehabilitation, 95*(1), 153-162. doi:10.1016/j.apmr.2013.07.022 [doi]

Hayes, S. C., Johansson, K., Stout, N. L., Prosnitz, R., Armer, J. M., Gabram, S., & Schmitz, K. H. (2012). Upper-body morbidity after breast cancer: incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. *Cancer, 118*(8 Suppl), 2237-2249. doi:10.1002/cncr.27467; 10.1002/cncr.27467

Hedeker, D., Toit, S. H. C. d., Demirtas, H., & Gibbons, R. D. (2018). A note on marginalization of regression parameters from mixed models of binary outcomes. *Biometrics, 74*(1), 354-361. doi:doi:10.1111/biom.12707

Hershman, D. L., Weimer, L. H., Wang, A., Kranwinkel, G., Brafman, L., Fuentes, D., . . . Crew, K. D. (2011). Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. *Breast cancer research and treatment, 125*(3), 767-774. doi:10.1007/s10549-010-1278-0; 10.1007/s10549-010-1278-0

Hunt, G. C. (2002). Peripheral Nerve Biomechanics: Application To Neuromobilization Approaches. *Physical Therapy Reviews, 7*(2), 111-121. doi:10.1179/108331902125001888

Jones, S., Holmes, F. A., O'Shaughnessy, J., Blum, J. L., Vukelja, S. J., McIntyre, K. J., . . . Savin, M. A. (2009). Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 27*(8), 1177-1183. doi:10.1200/JCO.2008.18.4028; 10.1200/JCO.2008.18.4028

Kelley, S., & Jull, G. (1998). Breast surgery and neural tissue mechanosensitivity. *The Australian journal of physiotherapy, 44*(1), 31-37.

Lundborg, G. (2000). Brain plasticity and hand surgery: an overview. *Journal of hand surgery (Edinburgh, Scotland), 25*(3), 242-252. doi:10.1054/jhsb.1999.0339

Moulin, D., Boulanger, A., Clark, A. J., Clarke, H., Dao, T., Finley, G. A., . . . Williamson, O. D. (2014). Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain research & management : the journal of the Canadian Pain Society = journal de la societe canadienne pour le traitement de la douleur, 19*(6), 328-335.

Nee, R. J., Vicenzino, B., Jull, G. A., Cleland, J. A., & Coppieters, M. W. (2012). Neural tissue management provides immediate clinically relevant benefits without harmful effects for patients with nerve-related neck and arm pain: a randomised trial. *Journal of Physiotherapy, 58*(1), 23-31. doi:https://doi.org/10.1016/S1836-9553(12)70069-3

Novak, C. B., & von der Heyde, R. L. (2013). Evidence and techniques in rehabilitation following nerve injuries. *Hand clinics, 29*(3), 383-392. doi:10.1016/j.hcl.2013.04.012; 10.1016/j.hcl.2013.04.012

Park, S. B., Lin, C. S., Krishnan, A. V., Friedlander, M. L., Lewis, C. R., & Kiernan, M. C. (2011). Early, progressive, and sustained dysfunction of sensory axons underlies paclitaxel-induced neuropathy. *Muscle & nerve, 43*(3), 367-374. doi:10.1002/mus.21874; 10.1002/mus.21874

Perez, C., Sanchez-Martinez, N., Ballesteros, A., Blanco, T., Collazo, A., Gonzalez, F., & Villoria, J. (2015). Prevalence of pain and relative diagnostic performance of screening tools for

neuropathic pain in cancer patients: A cross-sectional study. *European journal of pain (London, England), 19*(6), 752-761. doi:10.1002/ejp.598 [doi]

R: A Language and Environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN3-900051-07-0, URL http://www.R-Project.org.

Roche, H., Fumoleau, P., Spielmann, M., Canon, J. L., Delozier, T., Serin, D., . . . Asselain, B. (2006). Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 24*(36), 5664-5671. doi:10.1200/JCO.2006.07.3916

Schmid, A. B., Brunner, F., Luomajoki, H., Held, U., Bachmann, L. M., Kunzer, S., & Coppieters, M. W. (2009). Reliability of clinical tests to evaluate nerve function and mechanosensitivity of the upper limb peripheral nervous system. *BMC musculoskeletal disorders, 10*, 11-2474-2410-2411. doi:10.1186/1471-2474-10-11; 10.1186/1471-2474-10-11

Schmid, A. B., Elliott, J. M., Strudwick, M. W., Little, M., & Coppieters, M. W. (2012). Effect of splinting and exercise on intraneural edema of the median nerve in carpal tunnel syndrome--an MRI study to reveal therapeutic mechanisms. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society, 30*(8), 1343-1350. doi:10.1002/jor.22064; 10.1002/jor.22064

Schmid, A. B., Nee, R. J., & Coppieters, M. W. (2013). Reappraising entrapment neuropathies--mechanisms, diagnosis and management. *Manual therapy, 18*(6), 449-457. doi:10.1016/j.math.2013.07.006 [doi]

Seretny, M., Currie, G. L., Sena, E. S., Ramnarine, S., Grant, R., MacLeod, M. R., . . . Fallon, M. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain, 155*(12), 2461-2470. doi:10.1016/j.pain.2014.09.020; 10.1016/j.pain.2014.09.020

Smith, E. M., Pang, H., Cirrincione, C., Fleishman, S., Paskett, E. D., Ahles, T., . . . Alliance for Clinical Trials in, O. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *Jama, 309*(13), 1359-1367. doi:10.1001/jama.2013.2813; 10.1001/jama.2013.2813

Smoot, B., Boyd, B. S., Byl, N., & Dodd, M. (2014). Mechanosensitivity in the upper extremity following breast cancer treatment. *Journal of hand therapy : official journal of the American Society of Hand Therapists, 27*(1), 4-11. doi:10.1016/j.jht.2013.08.021; 10.1016/j.jht.2013.08.021

Stubblefield, M. D., McNeely, M. L., Alfano, C. M., & Mayer, D. K. (2012). A prospective surveillance model for physical rehabilitation of women with breast cancer: chemotherapy-induced peripheral neuropathy. *Cancer, 118*(8 Suppl), 2250-2260. doi:10.1002/cncr.27463; 10.1002/cncr.27463

Swain, S. M., Tang, G., Geyer, C. E., Jr., Rastogi, P., Atkins, J. N., Donnellan, P. P., . . . Wolmark, N. (2013). Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31*(26), 3197-3204. doi:10.1200/JCO.2012.48.1275; 10.1200/JCO.2012.48.1275

Upton, A. R., & McComas, A. J. (1973). The double crush in nerve entrapment syndromes. *Lancet (London, England), 2*(7825), 359-362. doi:S0140-6736(73)93196-6 [pii]

Walk, D., Sehgal, N., Moeller-Bertram, T., Edwards, R. R., Wasan, A., Wallace, M., . . . Backonja, M. M. (2009). Quantitative sensory testing and mapping: a review of nonautomated quantitative methods for examination of the patient with neuropathic pain. *The Clinical journal of pain, 25*(7), 632-640. doi:10.1097/AJP.0b013e3181a68c64; 10.1097/AJP.0b013e3181a68c64

TABLE 1. Demographics.

	Treatment (n=22)	Control (n=26)	p value
Age mean (SD)	56.3 (9.9)	53.0 (10.3)	0.26
Stage n (%)			
I	6 (27.2)	11 (42.3)	0.35
II	10 (45.4)	12 (46.1)	
III	6 (27.2)	3 (11.5)	
Cancer Side n (%)			
Right	8 (36.4)	11 (42.3)	0.87
Left	14 (63.6)	14 (53.8)	
Bilateral	none	1 (3.8)	
Surgery n (%)			
Lumpectomy	11 (50)	16 (61.5)	0.77
Single Mastectomy	8 (36.4)	7 (26.9)	
Bilateral Mastectomy	3 (13.6)	3 (11.5)	
Reconstruction n (%)	6 (27.3)	4 (15.4)	0.48
Radiation n (%)	15 (68.2)	21 (80.76)	0.5
Docetaxel n (%)			
FECD (6 rounds/3 taxane)	15 (68.2)	15 (57.7)	0.65
TC (4 rounds/all include taxane)	7 (31.1)	11 (42.3)	

TABLE 2. Physical Therapy Intervention.

	Treatment (n=22)	Control (n=26)	p value
NPRS number of visits (%)			
No pain	61 (70.1)	53 (51.0)	
1+ pain	26 (29.9)	51 (49.0)	p=0.05* (OR 0.41, 95% 0.17-1.01)
DASH median (Q1-Q3)	34 (31-45)	42 (33-52)	p=0.25
S-LANSS n(%)			
<12	73 (83.9)	77(74.0)	
>12	14(16.1)	27(26.0)	p=0.24
Vibration median (Q1-Q3)			
Left	0.23 (0.14-0.41)	0.14 (0.04-0.31)	p=0.43
Right	0.23 (0.14-0.41)	0.23 (0.04-0.41)	p=0.92
Pain Pressure (SD)	923 (383)	744 (285)	p=0.03*
Grip Dynamometry (SD)	27.2 (5.53)	21.8 (4.26)	p=<0.0001*

Table 2. shows the results from the mixed methods analysis and represents comparisons of all follow up assessments between treatment and control. Predictors for the odds ratio were treatment variable and follow-up time. Time variable analysis showed a significant decrease in pain as measured by the NPRS (OR 0.85, 95% CI 0.76-0.94; p=0.002) over time while both Pain pressure and grip had non-significant changes over time.

FIGURE 1.

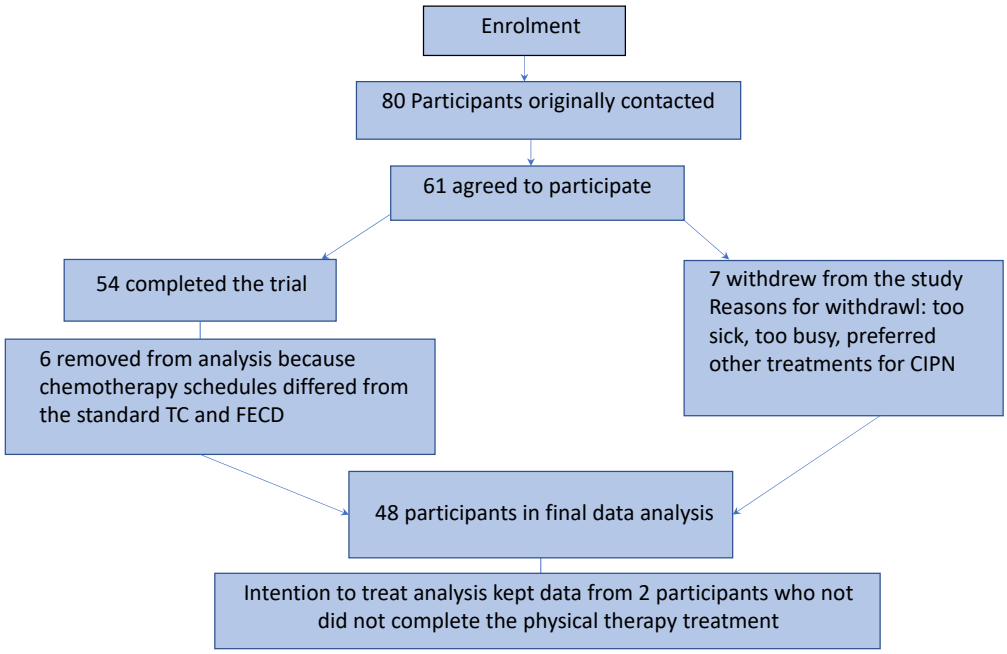


Figure 1. Consort diagram of enrolment. This figure pictorially represents the over-all participant contact for recruitment, enrolment, withdrawal rate including reasons for withdrawal as well as participants excluded from analysis and rational.

FIGURE 2.

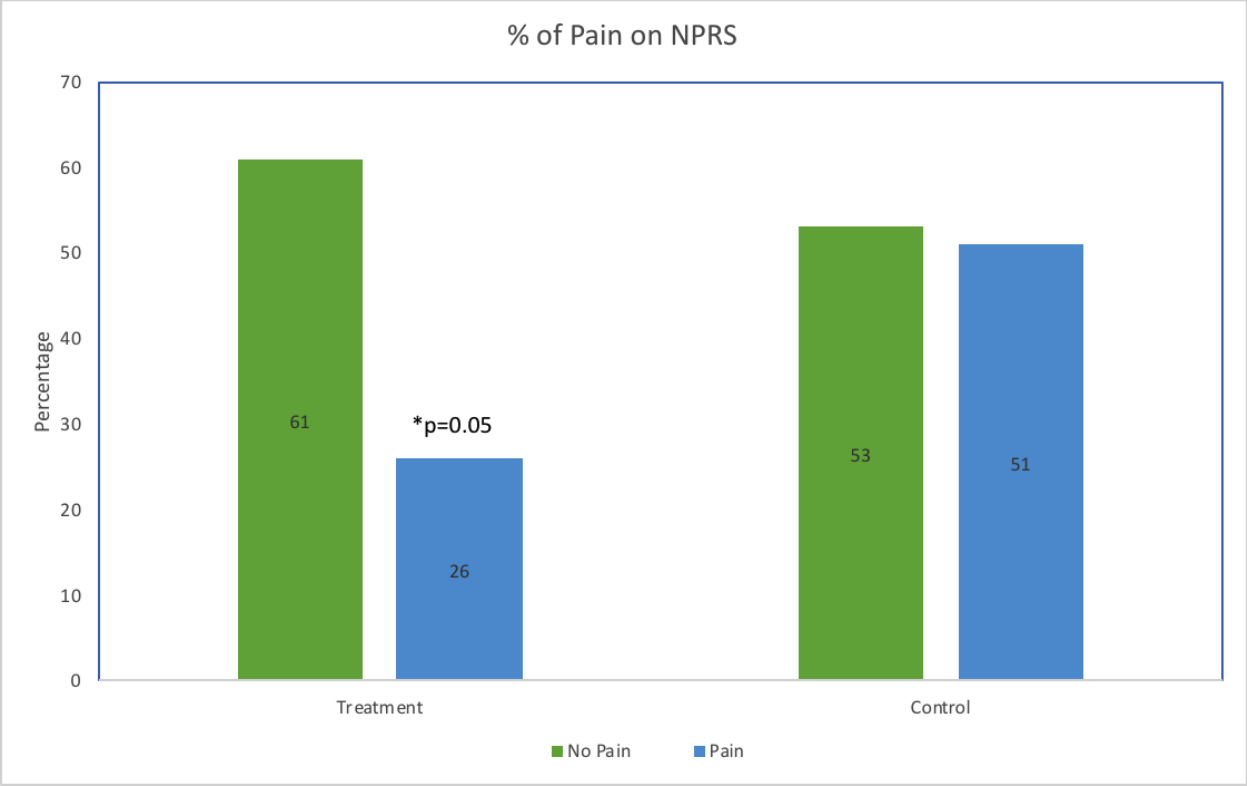


Figure 2. Percentage of pain. The bar graph indicates the percentage of pain for participants randomized to treatment (n=22) and control (n=26). Green bars indicate percentage of participants with no pain while the blue bars indicate percentage of participants with pain. Treatment and control are along the x-axis and percentage of pain is along the y axis. The treatment group had less pain (OR 0.41, 95% CI 0.17-1.01; p=0.05). Time variable analysis showed a significant decrease in pain over time as measured by the NPRS (OR 0.85, 95% CI 0.76-0.94; p=0.002). The numbers inside the bars represent the number of visits.

FIGURE 3.

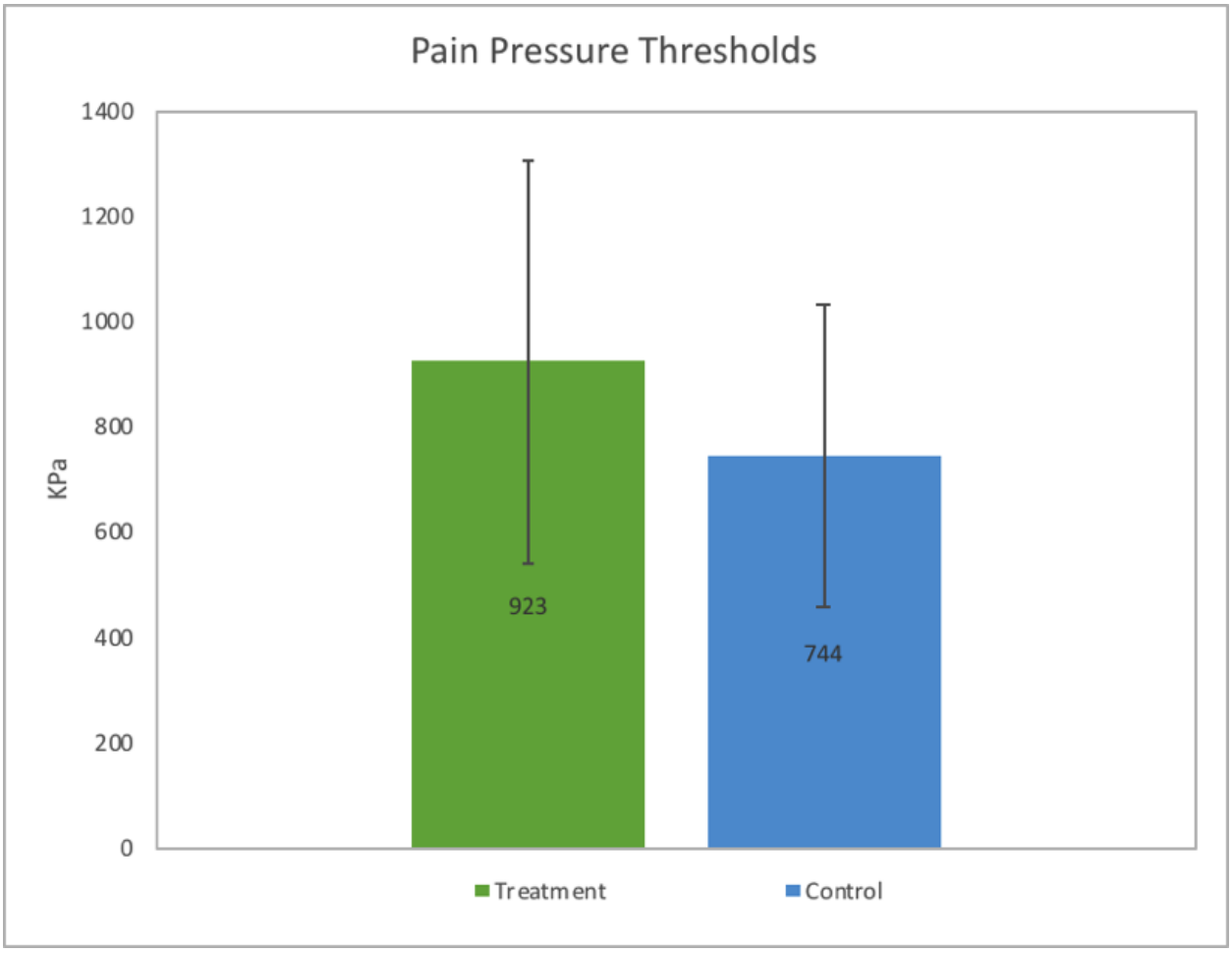


Figure 3. Pain pressure thresholds. The bar graph indicates the pain pressure thresholds for participants randomized to treatment (n=22) and control (n=26). The green bar indicates the average kilopascal (KPa) for pain pressure thresholds of all treatment participants over time, while the blue bar indicates average kilopascal (KPa) for controls. Treatment and control are along the x-axis and pressure (KPa) is along the y axis. The numbers inside the bars is the mean and the error bars represent the SD. The treatment group had higher pain pressure thresholds (p=0.03). Pain pressure had

non-significant changes over time, suggesting stability of this measure in the treatment group.

FIGURE 4.

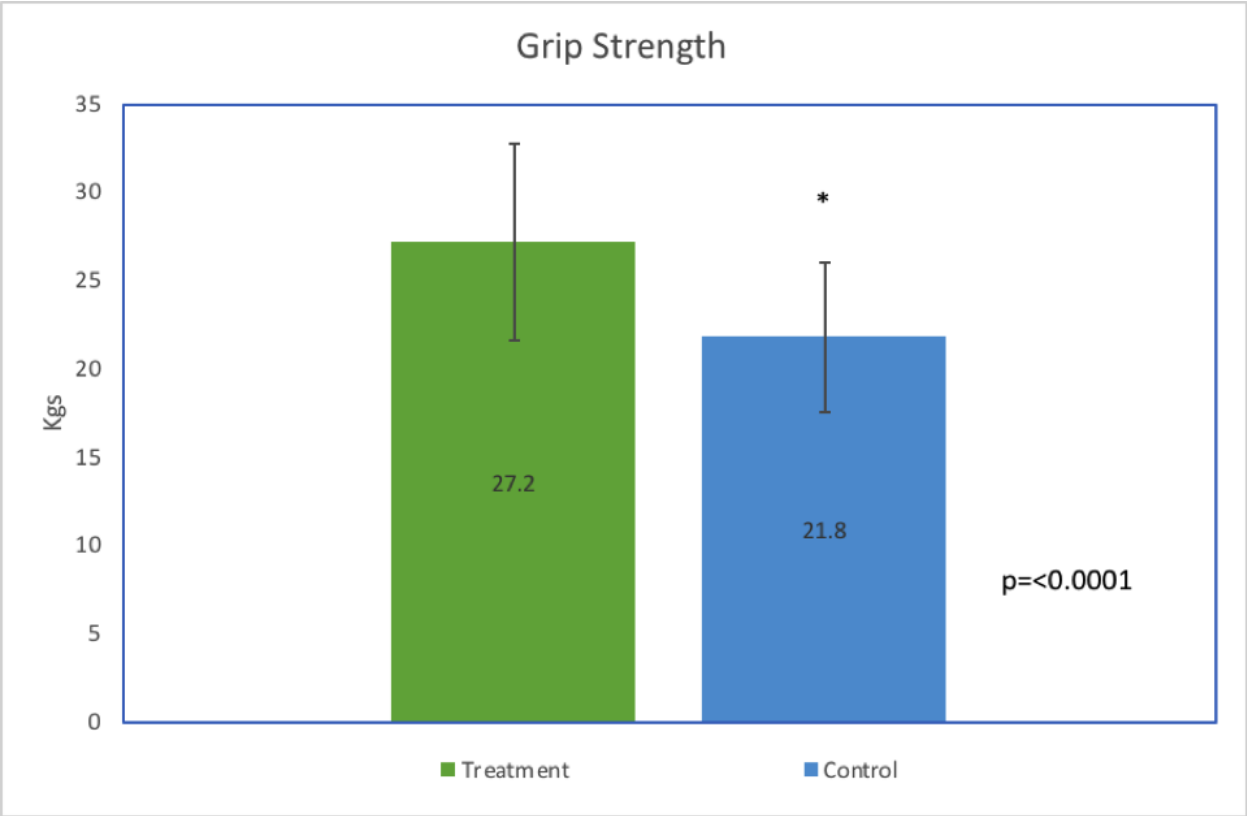


Figure 4. Grip strength. The bar graph indicates the average grip strength for all participants randomized to treatment (n=22) and control (n=26) over time. The green bar indicates the average force (Kgs) of all treatment participants, while the blue bar represents controls. Treatment and control are along the x-axis and force (Kgs) is along the y axis. The numbers inside the bars are the mean and the error bars represent the SD. The treatment group had higher grip strength ($p<0.0001$). Grip strength had non-significant changes over time, suggesting stability of this measure in the treatment group.

CHAPTER 4: Electro Acupuncture is not Recommended for Managing Chronic Neuropathic Pain in Chemotherapy Induced Peripheral Neuropathy: A double blind randomized controlled trial.

Running Head: Electro Acupuncture not recommended for CIPN

MY CONTRIBUTION TO THE MANUSCRIPT

The development of the acupuncture paper was a joint collaboration between Dr. Barbara Shay and myself. Dr. Marshall Pitz was instrumental in recruitment by obtaining permission to access the cancer registry. I completed the literature search, helped develop the protocol, assisted in grant writing, completed ethics applications to both the Health Research Ethics Board and Research Resource Impact Committee. I completed recruitment via phone, consented and assessed participants, and managed the project among the various team members. Janine Didyk administered the true and sham acupuncture. Pascal Lambert analyzed the data. I interpreted the results and prepared the manuscript for publication in a peer reviewed journal.

ABSTRACT

Purpose: Research on acupuncture for chemotherapy induced peripheral neuropathy (CIPN) treatment lacks important scientific standards that include homogenous populations, sham groups, and valid and reliable outcome measures. This prospective double-blind randomized controlled trial (RCT) sought to answer whether electro acupuncture (EA) could improve chronic neuropathic CIPN pain in breast cancer patients exposed to taxane chemotherapy compared to a sham control group.

Methods: 18 participants (10 treatment and 8 sham) were recruited from the cancer registry at CancerCare Manitoba. Primary outcome measure was the numeric pain rating scale (NPRS). Subjective questionnaires and Quantitative Sensory Testing (QST) were used to establish nerve pain and function for baseline and follow up post 6-week trial. Acupuncture treatment consisted of points ST36, LR3, and LI4 bilaterally x 30 minutes, once a week over 6 weeks. EA was applied to ST36 at 2Hz at maximum tolerance. Sham acupuncture using Streitberger Placebo Needles (Asiamed) included the same points and treatment parameters.

Results: Baseline NPRS scores were equal between the groups with sham median (Q1-Q3) 5.5 (4.75-6.0) and true 5.0 (3.5-7.75) NS. Post pain scores revealed a statistically significant and clinically relevant improvement for the sham group with a reduction in pain to 2.50 (2.0-3.0), p=0.04 compared to the true acupuncture group 4.25 (3.25-5.0) that demonstrated no clinical or statistical improvement.

Conclusion: This trial used best practice, incorporated a homogeneous population, used valid and reliable outcome measures, and sham controls. There is no evidence to suggest that EA works in this population.

KEY WORDS: chemotherapy induced peripheral neuropathy (CIPN), acupuncture, electro acupuncture, breast cancer

INTRODUCTION

Chemotherapy Induced Peripheral Neuropathy (CIPN) is a leading complaint among cancer survivors and can result in lasting symptoms of neuropathic pain or hypoesthesia (Sisignano, Baron, Scholich, & Geisslinger, 2014). Despite the prevalence and persistence of symptoms, there are currently few treatments available (Hershman et al., 2014). The majority of patients on chemotherapy treatment will seek Complementary Alternative Medicine (CAM) to assist with symptoms during and after cancer treatment (Richardson, Masse, Nanny, & Sanders, 2004; Sparber et al., 2000). CAM encompasses a variety of treatments ranging from homeopathy to mindfulness. A few of these treatments such as meditation and relaxation can be valuable, while others (such as acetyl-L-carnitine) have been shown to exacerbate CIPN symptoms (Hershman et al., 2013). Evidence of the benefit or harm of CAM treatments is difficult to determine as many of these treatments have not been scientifically tested (Han & Smith, 2013; Poupon et al., 2015; Sisignano et al., 2014). Acupuncture is part of CAM and a popular choice for many breast cancer patients. The National Institute of Health consensus statement in 1997 and a prospective randomized controlled trial for electro acupuncture (EA) and chemotherapy-induced emesis have led to increasing acceptance among cancer patients and the medical community ("Acupuncture," 1997; Cohen, Menter, & Hale, 2005; Shen et al., 2000). The efficacy for acupuncture specific to the treatment of cancer pain is limited. Further, the current research for acupuncture and CIPN treatment lack important scientific standards including homogenous populations, sham groups, valid and reliable outcome measures, reported acupuncture points, treatment time and duration (Y. Bao et al., 2014; Choi, Lee, Kim, Zaslawski, &

Ernst, 2012; Cohen et al., 2005; H. Lee, Schmidt, & Ernst, 2005; Paley, Tashani, Bagnall, & Johnson, 2011). This study sought to answer whether a combination of acupuncture and EA (used to strengthen the clinical response) could improve neuropathic pain CIPN symptoms in breast cancer patients exposed to taxane chemotherapy compared to a sham control group.

METHODS

Participants and Eligibility

Patients were recruited from the cancer registry at CancerCare Manitoba. All stage I-III, first cancer patients with primary breast cancer diagnosed in 2015 and 2016 that received docetaxel chemotherapy were contacted via letter. The letter indicated that an acupuncture trial was recruiting for the treatment of painful CIPN symptoms and contained contact information for the research coordinator. Participants were screened over the phone with the Self report of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire and a numeric pain rating scale (NPRS). A score >12 on the S-LANSS and an NPRS 3/10 or higher were eligible for participation to avoid the floor effect. See appendix E for the complete S-LANSS questionnaire. Exclusion criteria were co-morbid conditions that cause peripheral neuropathic symptoms, medical co-morbidities that are contraindications for acupuncture, lymphedema, pain not specific to fingers/toes, and pain not neuropathic in origin (SLANSS <12 and NPRS <3/10).

Protocol

Ethics approval was obtained from the Health Research Ethics Board (HREB) at the University of Manitoba (H2015:282) and the Research Resource Impact Committee at CancerCare Manitoba (2015:042). After consent, an initial assessment for baseline nerve function testing was completed.

Self-reported data and Quantitative Sensory Testing (QST) were used to establish nerve pain and function for baseline and the follow up post 6-week trial. Quantitative sensory testing (QST) is a valid, reliable and reproducible measure frequently used in research for diagnosing and assessing small fibre neuropathies such as CIPN (Arendt-Nielsen & Yarnitsky, 2009; Hershman et al., 2011). QST accurately measures somatosensory characteristics at specific time points and provides information on larger myelinated (Aβ), small thinly myelinated (Aδ), and unmyelinated (C-fibre) function or dysfunction. The most painful of either the fingers or toes was chosen for testing. Follow up assessment (blinded assessor) occurred 2-4 days after the six-week trial to repeat the nerve assessment and self-report questions. After the final assessment, those allocated to sham acupuncture were offered true acupuncture. Preliminary data analysis revealed statistically and clinically significant change in pain scores for the sham group, and the study was terminated.

Outcome Measures

1) Numeric Pain Rating Scale (NPRS) - was the primary outcome measure. A verbal description (0-10) on the intensity of CIPN pain on each visit was assessed. 0 indicates ‘no pain’ while 10 indicates ‘worst pain imaginable’. A minimum of 3/10 was required for study enrolment.

2) Self report version of the Leeds Assessment for Neuropathic Symptoms and Signs (S-LANSS) - is a valid, sensitive and specific questionnaire and was used to confirm the resolution of neuropathic pain and symptoms (Bennett, Smith, Torrance, & Potter, 2005). A score equal to or >12 was required for study enrolment to confirm presence of neuropathic symptoms, ensuring a relatively homogenous sample.

3) Participants' expectations for potential recovery with acupuncture treatment were recorded on initial assessment. Expectation is known to play a large role in treatment response and helped to confirm between group similarities.

4) Belief - a post treatment question whether the participant believed they were in the true versus sham acupuncture condition that was recorded on the final assessment.

5) Thermal cold pain thresholds (Neurosensory Analyzer TSAII, Medoc, Israel) - measured Aδ and C-fibre function. Increased sensitivity to thermal pain thresholds results in thermal hyperalgesia and has been described as a common feature of both neuropathic pain and painful CIPN. The TSA II thermode is attached to the tip of the palmar surface of the distal phalanx of the index finger or plantar surface of the big toe. Temperature is decreased by 0.1-degree Celsius (°C) increments until the participant presses a button indicating thermal pain. The test immediately stops when the participant presses the button and the temperature returns to baseline (32 °C). The participant is always in control and is never at risk for tissue damage (temperature limits are set to vary only from 0-50 °C. Thermal hyperalgesia is defined as a response of >18 °C.

6) Pressure/pain thresholds (pain pressure algometer) - was selected as a measure of central sensitization. A hand-held device (Somedic AB, Sweden) was applied

perpendicular to the left quadriceps muscle. The quadriceps muscle is distant from the source of pain and a lower tolerance to pressure suggests the possibility of central sensitization. Increasing pressure is applied until the participant determines that the sensation has changed from a feeling of pressure to a feeling of pain. The test stops when the participant presses the button indicating pain, and force (Kpa) is recorded.

The protocol was based on consensus recommendations for optimal treatment, sham controls and blinding from the International Acupuncture Research Forum, and the standards for reporting interventions in clinical trials of acupuncture (STRICTA) (Ma, 2004; MacPherson et al., 2002; A. White et al., 2008; A. R. White, Filshie, Cummings, & International Acupuncture Research, 2001; Zyloney et al., 2010). Both the outcome assessor and participant were blinded to the intervention groups. Random numbers were assigned to each group and envelopes containing treatment or sham were pre-randomized, sealed, and provided to the experienced acupuncturist. True acupuncture consisted of acupuncture points ST36, LR3, and LI4 bilaterally x 30 minutes, once a week over 6 weeks. EA was applied to ST36 where electrical current is transmitted through the needles with 2Hz at the maximum tolerated intensity (ES-130 Portable Japanese Electro-Acupuncture Device, UPC Medical Supplies Inc. South El Monte, CA, USA). These points were selected using STRICTA guidelines and points and treatment times previously shown to be effective (T. Bao, Zhang, Badros, & Lao, 2011; Donald, Tobin, & Stringer, 2011; MacPherson et al., 2010; MacPherson et al., 2002; Mayor, 2013; A. R. White et al., 2001; Wong & Sagar, 2006).

Sham acupuncture using Streitberger Placebo Needles (Asiamed) included the same points and treatment parameters, but the placebo needles do not penetrate the

skin and the current for EA was not turned on. Streitberger placebo needles are virtually indistinguishable from true acupuncture needles (Kleinhenz et al., 1999). The end of the needle is blunted so that it cannot penetrate the skin. The handle telescopes similar to magicians' 'fake dagger', and the illusion results in the participant thinking they received true acupuncture. Multiple sensory systems are misled as the participant feels the sharp 'pin-prick' sensation, sees the needle penetrating and the blinking green light from the electrical stimulus device, convincing the individual that real treatment has been provided. See appendix D for a description of the acupuncture points and experimental set up. Participants had painful CIPN symptoms in either the hands, the feet or both. The most painful of either the hands or feet was tested. As acupuncture is a systemic treatment, it was appropriate to select the most painful site for study and our outcomes were sensitive and specific to either the hands or the feet.

Data Analysis

NPRS values pre- and post-intervention between the treatment and control groups were compared using the Mann-Whitney test. S-LANSS values post-intervention were compared using the Fisher's exact test. Delta scores from pre-intervention to post-intervention assessments were calculated for cold pain scores and pain pressure scores. Independent t-tests were used to compare cold pain scores, whereas the Mann-Whitney test was used for pain pressure because the assumption of normality was not met. All analyses were run using the R project for statistical computing software version 3.4.1. (R. Development team, 2017).

RESULTS

Our initial cancer registry letter resulted in 40 phone calls. Of this, 19 female participants met the inclusion criteria and were invited to participate. Ineligibility of the interested participants was due primarily to other pain not defined as neuropathic in origin (S-LANSS<12). A second cancer registry letter for chemotherapy completed in 2017 was planned to increase enrolment, however, preliminary data analysis indicated treatment was ineffective and further enrolment was therefore unnecessary. One participant withdrew from the study after the first acupuncture treatment session as she believed her pain increased significantly with acupuncture. She had been randomized to the sham group and had only received placebo needles. Ten participants in true treatment and 8 in sham treatment completed the trial. To meet the minimum criteria of CIPN pain for 6 months, participants had to have completed their chemotherapy by October 2016. 16 of 18 participants completed chemotherapy in 2015 with the remaining 2 participants completing in 2016. Pain was primarily reported as being the worst in the feet (n=13) versus the hands (n=5).

1) Our primary outcome measure was the change in pain score. A change score of 2 for the NPRS is defined as clinically relevant (Farrar, Young, LaMoreaux, Werth, & Poole, 2001). Baseline NPRS scores were equal between the groups with sham median (Q1-Q3) 5.5 (4.75-6.0) and true 5.0 (3.5-7.75) NS. Post pain scores revealed a statistically significant and clinically relevant improvement for the sham group with a reduction in pain to 2.50 (2.0-3.0), p=0.04, compared to the true acupuncture group 4.25 (3.25-5.0) that demonstrated no clinical improvement. Figure 1. shows the median and IQR of true versus sham pain scores pre and post treatment.

2) SLANSS scores changed post-treatment. While everyone had to have a score >12 before the trial to define the pain as neuropathic, only one person continued to score >12 after sham treatment, indicating that 7 sham treatment individuals perceived their pain as being different (less neuropathic symptoms of burning, shooting, hypersensitivity). The true acupuncture group were more likely to maintain the description of pain being neuropathic in origin with 6/10 scoring >12. Comparison of the post treatment S-LANSS scores between the sham and true groups were not significant; however, the difference approached statistical significance (p=0.06). Thus, the data was trending that true EA had less effect on neuropathic pain descriptions compared with sham acupuncture.

3) Participants' expectations for recovery with acupuncture. At initial assessment, all 18 participants either believed acupuncture would help their symptoms (n=3 in treatment and n=1 in sham) or had heard it could help and were wanting to 'give it a try' (n=7 in treatment and n=7 in sham). Post treatment, when asked if acupuncture treatment helped their pain, 13 of 18 (72.2%) believed they were better. Of the 5 participants that felt their pain was not helped, 3 were in the treatment group and 2 were in the sham. Therefore, 70% of true (n= 7) and 75% of sham (n= 6) believed acupuncture had improved their pain. Figure 2A and Figure 2B plots the individual change scores of the participants in the true and sham groups. None of the participants were worse with the majority having decreased pain scores post-treatment compared to baseline.

4) True versus Sham treatment. One participant in the true acupuncture group believed they had received sham treatment, while two of the sham group were unsure of sham versus true acupuncture allocation.

5) Thermal Hyperalgesia. There was no difference in QST measures for changes in cold pain (p=0.64).

6) Pressure Algometry. There was no difference in pressure pain thresholds (p=0.18).

DISCUSSION

This EA trial demonstrates no benefit for the treatment of chronic neuropathic CIPN pain. Preliminary analysis confirmed that true acupuncture treatment was not resulting in improved pain scores or the expected placebo response. The treatment group only demonstrated a 15% pain reduction, which was unexpected. At minimum, it was expected that pain scores would be equal to sham acupuncture (pain reduction by 45%), even if true acupuncture was ineffective. We had concerns that EA potentially may be maintaining neuropathic pain. The Health Research Ethics Board was consulted, and it was agreed the study should be terminated. The inference was, at best, the treatment was ineffective; and, at worst, EA actually may be maintaining neuropathic pain.

Despite no statistically significant or clinically relevant change in pain for the treatment group, 70% subjectively reported that acupuncture treatment had helped their symptoms. The participants' recollection of the effectiveness of acupuncture contrasted with the QST and subjective questionnaire data. This highlights the importance of using valid and reliable outcome measures to monitor change over time. Individual reflection on experience and memory is not objective.

It may seem unlikely in a chronic pain state that the sham group improved by 45%. Likely, the observed pain reduction post sham treatment would not have persisted, and

their pain would have returned shortly after re-assessment. The placebo literature supports the dramatic improvements in the sham group and explains how this would be expected. Placebo research describes the power of expectation and hope in modulating neuro immune responses and the pain processing network. Central nervous system pain modulation affects the descending noxious inhibitory control system, the anterior cingulate cortex, amygdala, dorsal lateral prefrontal cortex, and the periaqueductal grey that is linked to the release of endogenous opioids and non-opioid neurotransmitters involved in analgesia. Depending on the clinical trial, placebo can account for 10-60% of the response. Specific to chronic pain states the literature varies between 26-45% (Peciña & Zubieta, 2015; Schedlowski, Enck, Rief, & Bingel, 2015). Expectations and beliefs have a known role in stimulating the same opioid pathways as acupuncture (Amanzio & Benedetti, 1999). Documenting this expectation in clinical trials can help explain the observed placebo response.

Animal models using acupuncture to produce anti-hyperalgesia help to interpret the possible physiological mechanisms and pathways that result in pain reduction. Specifically, (EA) is effective in diminishing cold hyperalgesia in rat models of chemotherapy-induced pain (Moon et al., 2014). Moon and colleagues showed that the opioid pathway was responsible by using the opioid receptor antagonist (naloxone) which negated the effects of EA in this pain model. EA effectively diminished hyperalgesia/allodynia in rats induced with paclitaxel neuropathy, and μ, δ, and k opioid receptors were responsible for the anti-hyperalgesic response (Meng et al., 2011). Additional rat models of neuropathic pain have confirmed that mechanical allodynia is relieved by 2-10 Hz EA and confirmed with antagonists that spinal μ and δ opioid

receptors mediate this anti-nociceptive effect (Hwang, Min, Kim, Na, & Park, 2002; Kim, Min, Na, & Park, 2004; Sun et al., 2004).

EA has also been shown to inhibit inflammatory mediators in the spinal cord after spinal nerve ligation (Lau, Chan, Zhang, Yung, & Zhang, 2008). EA has been shown to stimulate the production of nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) in rats and rabbits (J. Chen et al., 2007; Y. S. Chen et al., 2001; La, Jalali, & Shami, 2005). These neurotrophic factors are important in stimulating the growth cone and promoting neuro regeneration after injury. While there is encouragement for the use of acupuncture/EA in animal models of pain, there is limited evidence from human clinical trials. Many systematic reviews have evaluated whether cancer specific pain can be treated with acupuncture (Y. Bao et al., 2014; Choi et al., 2012; Franconi, Manni, Schroder, Marchetti, & Robinson, 2013; G. S. Lee et al., 2003; Paley et al., 2011). Unfortunately, reviews recognize that the majority of studies are of low methodological quality, lack proper blinding, have high risk of bias, and have no control groups.

One article, in particular, is consistently identified in many reviews to be of high methodological quality, low risk of bias, with proper randomization (Alimi et al., 2003). Alimi and colleagues published a blinded, prospective, randomized controlled trial (RCT) in the Journal of Clinical Oncology, and found that auricular acupuncture was effective in treating chronic central and peripheral neuropathic pain (measured by the VAS pain scale and average electrical potential difference). This study had a heterogeneous sample population (included head and neck, breast, lung and other cancers), included all stages of cancer (including metastatic disease), treated any

painful site in the body (average of 6 different painful sites per person), lacked validated outcome measures (the effect relating to pain by measuring the electrical potential difference of the ear with an electrical voltmeter has not been validated), used no outcome measures to distinguish the type of pain treated (i.e. neuropathic, nociceptive, inflammatory), and weak inclusion criteria (pain only had to be stable for one month). Their primary outcome measure was average pain at day 60 after 2 acupuncture treatments one month apart. The structure of the methods raises the possibility that improvements in pain scores could easily occur with passing time.

Another CIPN pilot study used nerve conduction studies (NCS) as the primary outcome measure on the effectiveness of acupuncture (Schroeder, Meyer-Hamme, & Epplee, 2012). The results demonstrated that acupuncture improved Aα fibres' velocity and amplitude signals, and that these improvements persisted 3 months post acupuncture treatment. Of significance here is that CIPN is a small fibre neuropathy affecting some Aβ, but mostly small thinly myelinated Aδ and unmyelinated C fibres, and nerve conduction studies are neither specific nor sensitive for evaluation of small fibre function. Our study used Quantitative sensory testing (QST) to provide quantitative nerve sensation data in addition to subjective reports of pain. QST is a quantitative, reliable and reproducible measure for diagnosing small fibre neuropathies (Aδ and C fibres) when adherence to protocol and attentiveness of the participant is maintained. QST can also quantify larger Aβ fibre function. CIPN symptoms begin as a small fibre neuropathy, and even small subclinical changes can be quantified with repeated measures of QST. (Backonja et al., 2009; Moloney, Hall, O'Sullivan, & Doody, 2011;

Rolke et al., 2006). Our study found no improvement to thermal pain or pressure pain thresholds with acupuncture.

In agreement with our results was an EA trial that found treatment was equal to placebo for CIPN (Rostock et al., 2013). Unfortunately, the methods chosen (specifically the treatment schedule, EA dosage time and frequency at 50 Hz) are not comparable to other animal/human studies (Sluka, Bjordal, Marchand, & Rakel, 2013; Somers & Clemente, 2006, 2009). The subjective CIPN complaints of the participants also differed substantially with some having pain, numbness, paresthesia, or functional impairments in the hands or feet. In addition, the inclusion criteria in the Rostock study allowed for multiple cancers, multiple chemotherapy regimens, and treatment at different time points post chemotherapy; that is, substantial heterogeneity, thus making it difficult to determine efficacy.

Low frequency (2-4 Hz) and high frequency (100 Hz) EA are established frequencies used in research and clinical practice and known to stimulate different pain modulation pathways (Sluka et al., 2013; Somers & Clemente, 2006, 2009). The optimal frequency is thought to activate endogenous opioid and descending noxious inhibitory control (DNIC) by stimulating Aδ fibres that, in turn, release endorphins and serotonin in the brain (DeSantana, Walsh, Vance, Rakel, & Sluka, 2008; Ma, 2004; Sung et al., 2004).

The Clinical Oncology Society of Australia published a position statement on complementary alternative medicine (CAM) identifying the growing acceptance among patients and the urgent need for clinicians to support research to clarify the potential benefit or harm, and define the role in cancer care (Braun et al., 2014). With patients

seeking CAM, evidence for use in cancer symptom management is required to assess the benefits and risks.

In terms of this current study, strict inclusion criteria ensured homogeneity, clearly defined methods allowed for repeatability, and acupuncture treatments selected from previous studies shown to be effective were employed. Both the participant and assessor were blinded to the treatment, and sham controls were used. The small sample size offers the possibility that the observed differences may be due to random effect although we suggest that true EA imparts no evidence of effect.

CONCLUSION

This prospective double-blind RCT used best practice and STRICTA guidelines for EA incorporating a homogeneous population, valid and reliable outcome measures, and sham controls. We believe that this current study demonstrates that patients should not seek EA treatment for neuropathic pain due to CIPN.

REFERENCES

Acupuncture. (1997). *NIH consensus statement, 15*(5), 1-34.

Alimi, D., Rubino, C., Pichard-Leandri, E., Fermand-Brule, S., Dubreuil-Lemaire, M. L., & Hill, C. (2003). Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 21*(22), 4120-4126. doi:10.1200/JCO.2003.09.011

Amanzio, M., & Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci, 19*(1), 484-494.

Arendt-Nielsen, L., & Yarnitsky, D. (2009). Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *The journal of pain : official journal of the American Pain Society, 10*(6), 556-572. doi:10.1016/j.jpain.2009.02.002; 10.1016/j.jpain.2009.02.002

Backonja, M. M., Walk, D., Edwards, R. R., Sehgal, N., Moeller-Bertram, T., Wasan, A., . . . Wallace, M. (2009). Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. *The Clinical journal of pain, 25*(7), 641-647. doi:10.1097/AJP.0b013e3181a68c7e; 10.1097/AJP.0b013e3181a68c7e

Bao, T., Zhang, R., Badros, A., & Lao, L. (2011). Acupuncture treatment for bortezomib-induced peripheral neuropathy: a case report. *Pain research and treatment, 2011*, 920807. doi:10.1155/2011/920807; 10.1155/2011/920807

Bao, Y., Kong, X., Yang, L., Liu, R., Shi, Z., Li, W., . . . Hou, W. (2014). Complementary and alternative medicine for cancer pain: an overview of systematic reviews. *Evidence-based complementary and alternative medicine : eCAM, 2014*, 170396. doi:10.1155/2014/170396; 10.1155/2014/170396

Bennett, M. I., Smith, B. H., Torrance, N., & Potter, J. (2005). The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *The journal of pain : official journal of the American Pain Society, 6*(3), 149-158. doi:10.1016/j.jpain.2004.11.007

Braun, L., Harris, J., Katris, P., Cain, M., Dhillon, H., Koczwara, B., . . . Robotin, M. (2014). Clinical Oncology Society of Australia position statement on the use of complementary and alternative medicine by cancer patients. *Asia-Pacific journal of clinical oncology, 10*(4), 289-296. doi:10.1111/ajco.12227; 10.1111/ajco.12227

Chen, J., Qi, J. G., Zhang, W., Zhou, X., Meng, Q. S., Zhang, W. M., . . . Wang, T. H. (2007). Electro-acupuncture induced NGF, BDNF and NT-3 expression in spared L6 dorsal root ganglion in cats subjected to removal of adjacent ganglia. *Neuroscience research, 59*(4), 399-405. doi:10.1016/j.neures.2007.08.006

Chen, Y. S., Yao, C. H., Chen, T. H., Lin, J. G., Hsieh, C. L., Lin, C. C., . . . Tsai, C. C. (2001). Effect of acupuncture stimulation on peripheral nerve regeneration using silicone rubber chambers. *The American Journal of Chinese Medicine, 29*(3-4), 377-385. doi:10.1142/S0192415X01000393

Choi, T. Y., Lee, M. S., Kim, T. H., Zaslawski, C., & Ernst, E. (2012). Acupuncture for the treatment of cancer pain: a systematic review of randomised clinical trials. *Supportive care in*

cancer : official journal of the Multinational Association of Supportive Care in Cancer, 20(6), 1147-1158. doi:10.1007/s00520-012-1432-9; 10.1007/s00520-012-1432-9

Cohen, A. J., Menter, A., & Hale, L. (2005). Acupuncture: role in comprehensive cancer care--a primer for the oncologist and review of the literature. *Integrative cancer therapies, 4*(2), 131-143. doi:10.1177/1534735405276419

DeSantana, J. M., Walsh, D. M., Vance, C., Rakel, B. A., & Sluka, K. A. (2008). Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. *Current rheumatology reports, 10*(6), 492-499.

Donald, G. K., Tobin, I., & Stringer, J. (2011). Evaluation of acupuncture in the management of chemotherapy-induced peripheral neuropathy. *Acupuncture in medicine : journal of the British Medical Acupuncture Society, 29*(3), 230-233. doi:10.1136/acupmed.2011.010025; 10.1136/acupmed.2011.010025

Farrar, J. T., Young, J. P., Jr., LaMoreaux, L., Werth, J. L., & Poole, R. M. (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain, 94*(2), 149-158.

Franconi, G., Manni, L., Schroder, S., Marchetti, P., & Robinson, N. (2013). A systematic review of experimental and clinical acupuncture in chemotherapy-induced peripheral neuropathy. *Evidence-based complementary and alternative medicine : eCAM, 2013*, 516916. doi:10.1155/2013/516916; 10.1155/2013/516916

Han, Y., & Smith, M. T. (2013). Pathobiology of cancer chemotherapy-induced peripheral neuropathy (CIPN). *Frontiers in pharmacology, 4*, 156. doi:10.3389/fphar.2013.00156 [doi]

Hershman, D. L., Lacchetti, C., Dworkin, R. H., Lavoie Smith, E. M., Bleeker, J., Cavaletti, G., . . . American Society of Clinical, O. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 32*(18), 1941-1967. doi:10.1200/JCO.2013.54.0914; 10.1200/JCO.2013.54.0914

Hershman, D. L., Unger, J. M., Crew, K. D., Minasian, L. M., Awad, D., Moinpour, C. M., . . . Albain, K. S. (2013). Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31*(20), 2627-2633. doi:10.1200/JCO.2012.44.8738; 10.1200/JCO.2012.44.8738

Hershman, D. L., Weimer, L. H., Wang, A., Kranwinkel, G., Brafman, L., Fuentes, D., . . . Crew, K. D. (2011). Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. *Breast cancer research and treatment, 125*(3), 767-774. doi:10.1007/s10549-010-1278-0; 10.1007/s10549-010-1278-0

Hwang, B. G., Min, B. I., Kim, J. H., Na, H. S., & Park, D. S. (2002). Effects of electroacupuncture on the mechanical allodynia in the rat model of neuropathic pain. *Neuroscience letters, 320*(1-2), 49-52.

Kim, J. H., Min, B. I., Na, H. S., & Park, D. S. (2004). Relieving effects of electroacupuncture on mechanical allodynia in neuropathic pain model of inferior caudal trunk injury in rat: mediation by spinal opioid receptors. *Brain research, 998*(2), 230-236.

Kleinhenz, J., Streitberger, K., Windeler, J., Gussbacher, A., Mavridis, G., & Martin, E. (1999). Randomised clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendinitis. *Pain, 83*(2), 235-241.

La, J. L., Jalali, S., & Shami, S. A. (2005). Morphological studies on crushed sciatic nerve of rabbits with electroacupuncture or diclofenac sodium treatment. *The American Journal of Chinese Medicine, 33*(4), 663-669. doi:10.1142/S0192415X05003259

Lau, W. K., Chan, W. K., Zhang, J. L., Yung, K. K., & Zhang, H. Q. (2008). Electroacupuncture inhibits cyclooxygenase-2 up-regulation in rat spinal cord after spinal nerve ligation. *Neuroscience, 155*(2), 463-468. doi:10.1016/j.neuroscience.2008.06.016; 10.1016/j.neuroscience.2008.06.016

Lee, G. S., Han, J. B., Shin, M. K., Hong, M. C., Kim, S. W., Min, B. I., & Bae, H. (2003). Enhancement of electroacupuncture-induced analgesic effect in cholecystokinin-A receptor deficient rats. *Brain research bulletin, 62*(2), 161-164.

Lee, H., Schmidt, K., & Ernst, E. (2005). Acupuncture for the relief of cancer-related pain--a systematic review. *European journal of pain (London, England), 9*(4), 437-444. doi:10.1016/j.ejpain.2004.10.004

Ma, S. X. (2004). Neurobiology of Acupuncture: Toward CAM. *Evidence-based complementary and alternative medicine : eCAM, 1*(1), 41-47. doi:10.1093/ecam/neh017

MacPherson, H., Altman, D. G., Hammerschlag, R., Li, Y., Wu, T., White, A., . . . Group, S. R. (2010). Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *Acupuncture in medicine : journal of the British Medical Acupuncture Society, 28*(2), 83-93. doi:10.1136/aim.2009.001370 [doi]

MacPherson, H., White, A., Cummings, M., Jobst, K. A., Rose, K., Niemtzow, R. C., & Group, S. (2002). Standards for Reporting Interventions in Controlled Trials of Acupuncture: the STRICTA recommendations. *Journal of alternative and complementary medicine (New York, N.Y.), 8*(1), 85-89. doi:10.1089/107555302753507212 [doi]

Mayor, D. (2013). An exploratory review of the electroacupuncture literature: clinical applications and endorphin mechanisms. *Acupuncture in medicine : journal of the British Medical Acupuncture Society, 31*(4), 409-415. doi:10.1136/acupmed-2013-010324; 10.1136/acupmed-2013-010324

Meng, X., Zhang, Y., Li, A., Xin, J., Lao, L., Ren, K., . . . Zhang, R. X. (2011). The effects of opioid receptor antagonists on electroacupuncture-produced anti-allodynia/hyperalgesia in rats with paclitaxel-evoked peripheral neuropathy. *Brain research, 1414*, 58-65. doi:10.1016/j.brainres.2011.08.004; 10.1016/j.brainres.2011.08.004

Moloney, N. A., Hall, T. M., O'Sullivan, T. C., & Doody, C. M. (2011). Reliability of thermal quantitative sensory testing of the hand in a cohort of young, healthy adults. *Muscle & nerve, 44*(4), 547-552. doi:10.1002/mus.22121; 10.1002/mus.22121

Moon, H. J., Lim, B. S., Lee, D. I., Ye, M. S., Lee, G., Min, B. I., . . . Kim, S. K. (2014). Effects of electroacupuncture on oxaliplatin-induced neuropathic cold hypersensitivity in rats. *The journal of physiological sciences : JPS, 64*(2), 151-156. doi:10.1007/s12576-013-0297-0; 10.1007/s12576-013-0297-0

Paley, C. A., Tashani, O. A., Bagnall, A. M., & Johnson, M. I. (2011). A Cochrane systematic review of acupuncture for cancer pain in adults. *BMJ supportive & palliative care, 1*(1), 51-55. doi:10.1136/bmjspcare-2011-000022; 10.1136/bmjspcare-2011-000022

Peciña, M., & Zubieta, J.-K. (2015). Molecular Mechanisms of Placebo Responses In Humans. *Molecular psychiatry, 20*(4), 416-423. doi:10.1038/mp.2014.164

Poupon, L., Kerckhove, N., Vein, J., Lamoine, S., Authier, N., Busserolles, J., & Balayssac, D. (2015). Minimizing chemotherapy-induced peripheral neuropathy: preclinical and clinical development of new perspectives. *Expert opinion on drug safety, 14*(8), 1269-1282. doi:10.1517/14740338.2015.1056777 [doi]

R: A Language and Envoironment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN3-900051-07-0, URL http://www.R-project.org.

Richardson, M. A., Masse, L. C., Nanny, K., & Sanders, C. (2004). Discrepant views of oncologists and cancer patients on complementary/alternative medicine. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 12*(11), 797-804. doi:10.1007/s00520-004-0677-3

Rolke, R., Magerl, W., Campbell, K. A., Schalber, C., Caspari, S., Birklein, F., & Treede, R. D. (2006). Quantitative sensory testing: a comprehensive protocol for clinical trials. *European journal of pain (London, England), 10*(1), 77-88. doi:10.1016/j.ejpain.2005.02.003

Rostock, M., Jaroslawski, K., Guethlin, C., Ludtke, R., Schroder, S., & Bartsch, H. H. (2013). Chemotherapy-induced peripheral neuropathy in cancer patients: a four-arm randomized trial on the effectiveness of electroacupuncture. *Evidence-based complementary and alternative medicine : eCAM, 2013*, 349653. doi:10.1155/2013/349653; 10.1155/2013/349653

Schedlowski, M., Enck, P., Rief, W., & Bingel, U. (2015). Neuro-Bio-Behavioral Mechanisms of Placebo and Nocebo Responses: Implications for Clinical Trials and Clinical Practice. *Pharmacol Rev, 67*(3), 697-730. doi:10.1124/pr.114.009423

Schroeder, S., Meyer-Hamme, G., & Epplee, S. (2012). Acupuncture for chemotherapy-induced peripheral neuropathy (CIPN): a pilot study using neurography. *Acupuncture in medicine : journal of the British Medical Acupuncture Society, 30*(1), 4-7. doi:10.1136/acupmed-2011-010034; 10.1136/acupmed-2011-010034

Shen, J., Wenger, N., Glaspy, J., Hays, R. D., Albert, P. S., Choi, C., & Shekelle, P. G. (2000). Electroacupuncture for control of myeloablative chemotherapy-induced emesis: A randomized controlled trial. *Jama, 284*(21), 2755-2761.

Sisignano, M., Baron, R., Scholich, K., & Geisslinger, G. (2014). Mechanism-based treatment for chemotherapy-induced peripheral neuropathic pain. *Nature reviews.Neurology, 10*(12), 694-707. doi:10.1038/nrneurol.2014.211 [doi]

Sluka, K. A., Bjordal, J. M., Marchand, S., & Rakel, B. A. (2013). What makes transcutaneous electrical nerve stimulation work? Making sense of the mixed results in the clinical literature. *Physical therapy, 93*(10), 1397-1402. doi:10.2522/ptj.20120281; 10.2522/ptj.20120281

Somers, D. L., & Clemente, F. R. (2006). Transcutaneous electrical nerve stimulation for the management of neuropathic pain: the effects of frequency and electrode position on

prevention of allodynia in a rat model of complex regional pain syndrome type II. *Physical therapy, 86*(5), 698-709.

Somers, D. L., & Clemente, F. R. (2009). Contralateral high or a combination of high- and low-frequency transcutaneous electrical nerve stimulation reduces mechanical allodynia and alters dorsal horn neurotransmitter content in neuropathic rats. *The journal of pain : official journal of the American Pain Society, 10*(2), 221-229. doi:10.1016/j.jpain.2008.08.008; 10.1016/j.jpain.2008.08.008

Sparber, A., Bauer, L., Curt, G., Eisenberg, D., Levin, T., Parks, S., . . . Wootton, J. (2000). Use of complementary medicine by adult patients participating in cancer clinical trials. *Oncology nursing forum, 27*(4), 623-630.

Sun, R. Q., Wang, H. C., Wan, Y., Jing, Z., Luo, F., Han, J. S., & Wang, Y. (2004). Suppression of neuropathic pain by peripheral electrical stimulation in rats: mu-opioid receptor and NMDA receptor implicated. *Experimental neurology, 187*(1), 23-29. doi:10.1016/j.expneurol.2003.12.011

Sung, H. J., Kim, Y. S., Kim, I. S., Jang, S. W., Kim, Y. R., Na, D. S., . . . Ko, J. (2004). Proteomic analysis of differential protein expression in neuropathic pain and electroacupuncture treatment models. *Proteomics, 4*(9), 2805-2813. doi:10.1002/pmic.200300821

White, A., Cummings, M., Barlas, P., Cardini, F., Filshie, J., Foster, N. E., . . . Witt, C. (2008). Defining an adequate dose of acupuncture using a neurophysiological approach--a narrative review of the literature. *Acupuncture in medicine : journal of the British Medical Acupuncture Society, 26*(2), 111-120.

White, A. R., Filshie, J., Cummings, T. M., & International Acupuncture Research, F. (2001). Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding. *Complementary therapies in medicine, 9*(4), 237-245.

Wong, R., & Sagar, S. (2006). Acupuncture treatment for chemotherapy-induced peripheral neuropathy--a case series. *Acupuncture in medicine : journal of the British Medical Acupuncture Society, 24*(2), 87-91.

Zyloney, C. E., Jensen, K., Polich, G., Loiotile, R. E., Cheetham, A., LaViolette, P. S., . . . Kong, J. (2010). Imaging the functional connectivity of the Periaqueductal Gray during genuine and sham electroacupuncture treatment. *Molecular pain, 6*, 80-8069-8066-8080. doi:10.1186/1744-8069-6-80; 10.1186/1744-8069-6-80

FIGURES

FIGURE 1.

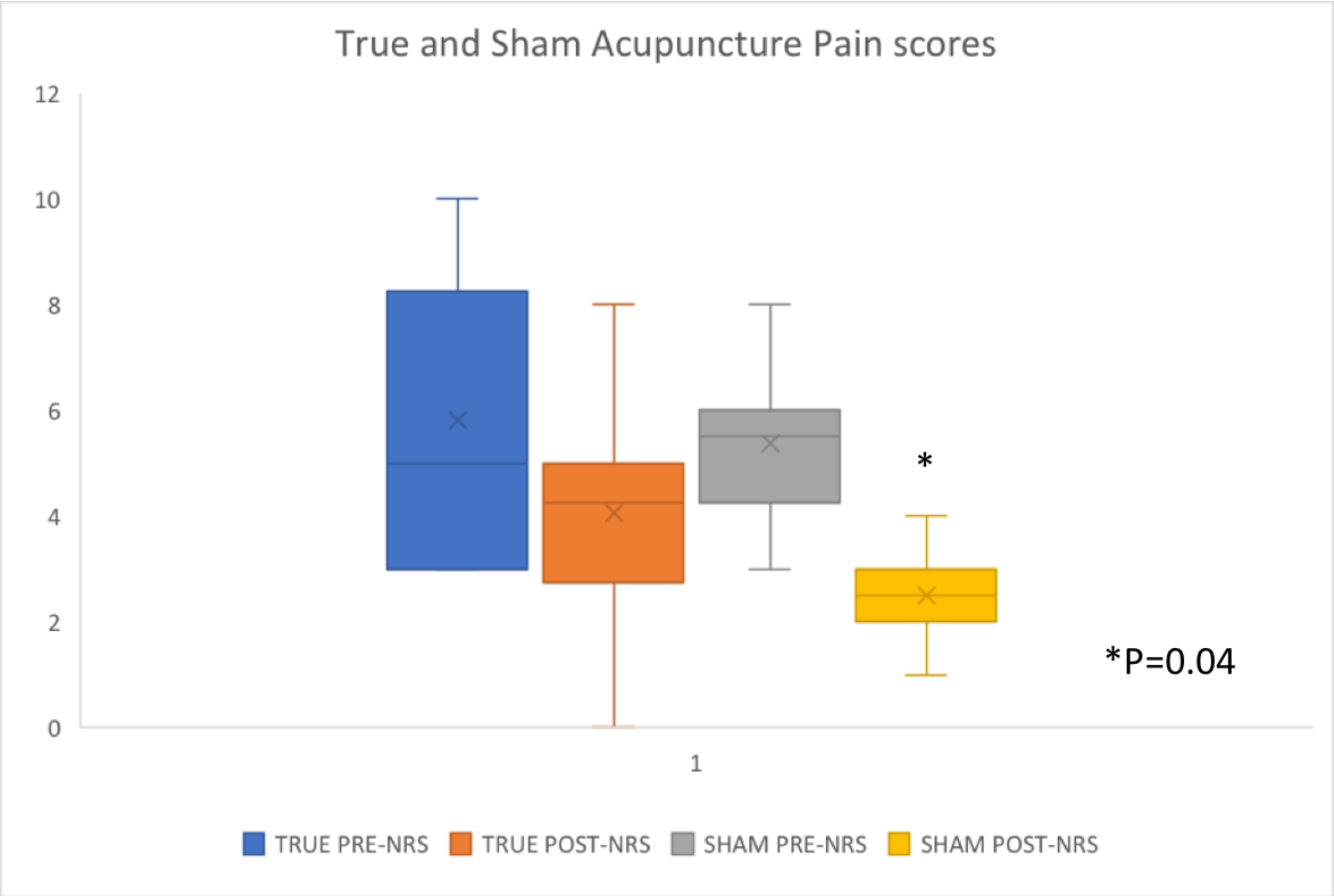


FIGURE 1. Pre and post treatment pain scores. The box and whisker plots indicate the pain scores for participants randomized to either true (n=10) or sham (n=8) acupuncture. The line represents the median score. The boxes indicate the 25th and 75th percentile and the whiskers are the highest and lowest values. The values along the y axis are NPRS scores from 0-10 where 0=no pain and 10= the worst pain imaginable.

FIGURE 2.

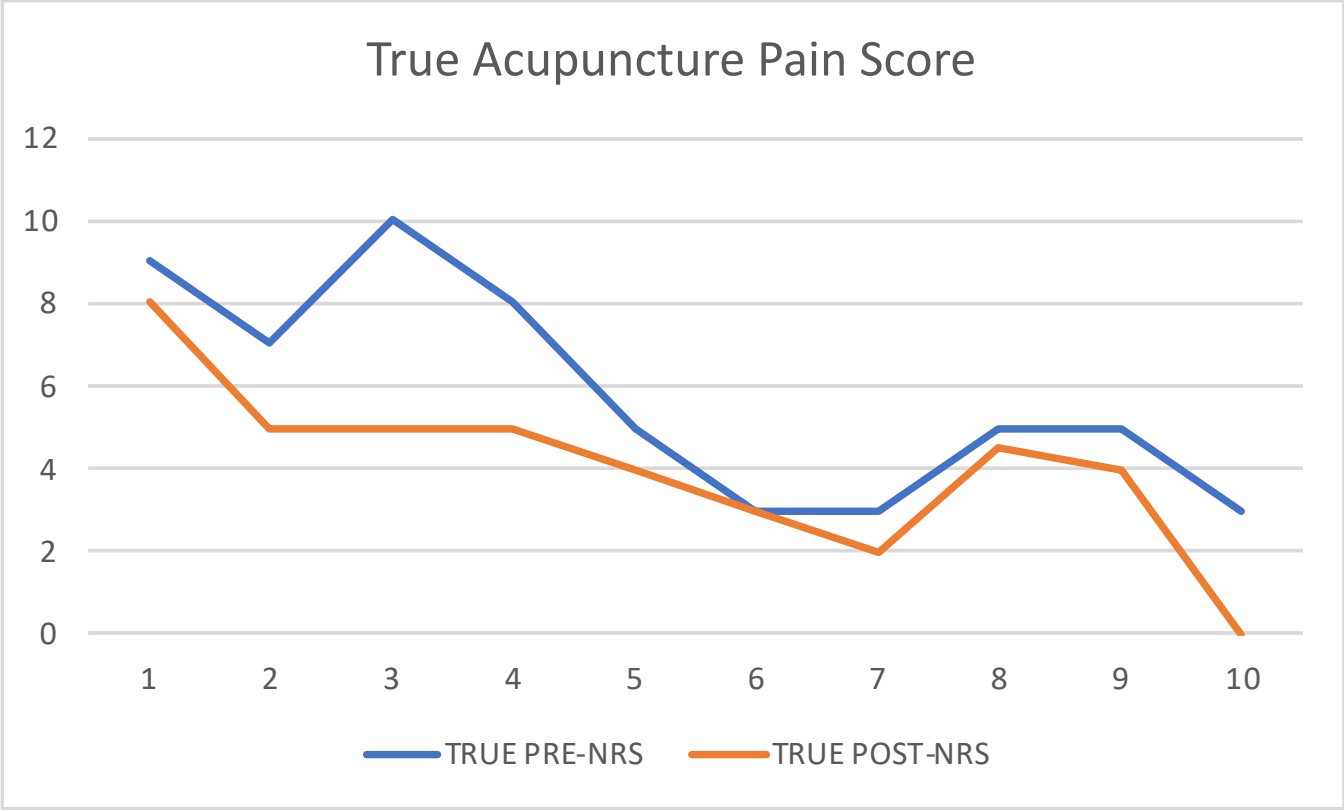


FIGURE 2A. Pre and post treatment pain scores. The line graph indicates the pain scores for participants randomized to true (n=10) acupuncture. The blue line represents the pre-treatment NPRS score. The orange line represents post-treatment NPRS scores. Participants are along the x-axis and NPRS scores are along the y axis. The NPRS ranks pain from 0-10 where 0=no pain and 10= the worst pain imaginable.

FIGURE 2B.

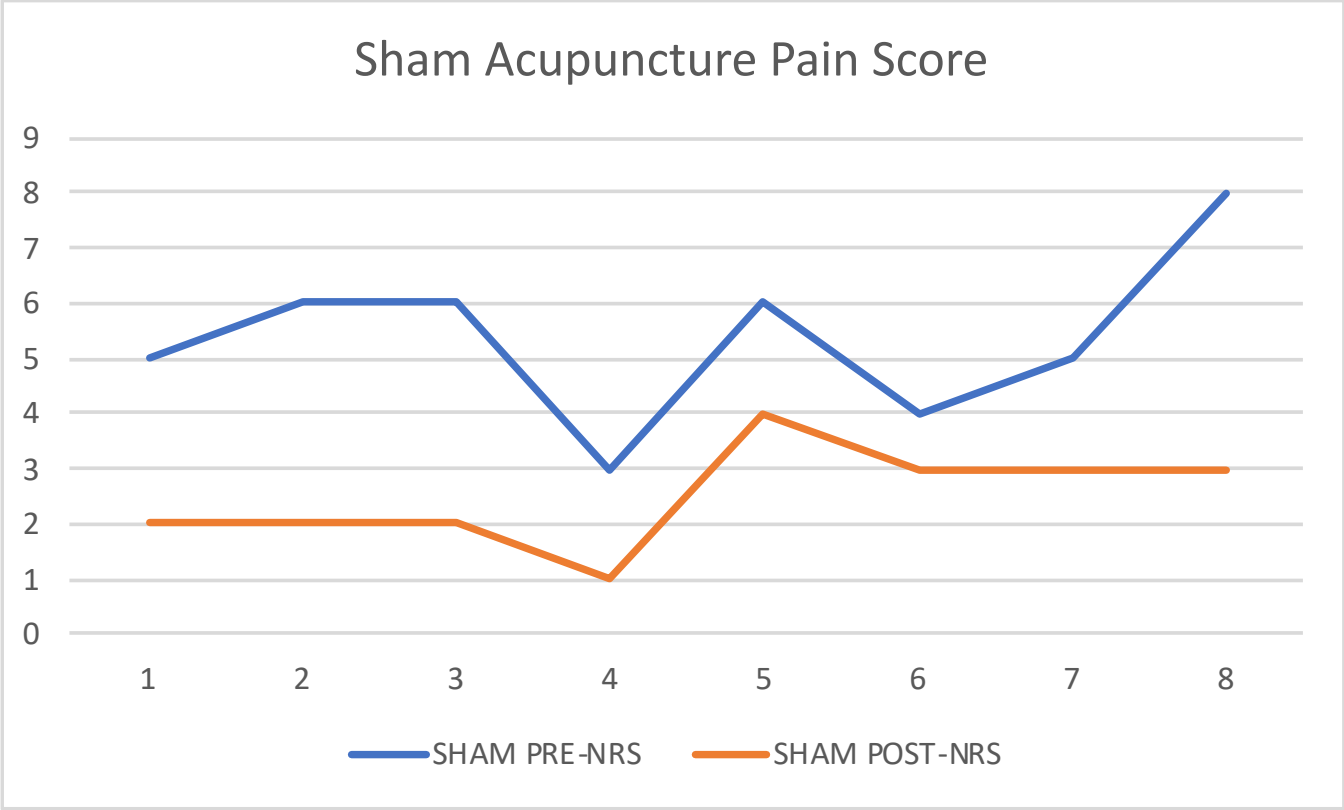


FIGURE 2B. Pre and post sham pain scores. The line graph indicates the pain scores for participants randomized to sham (n=8) acupuncture. The blue line represents the pre-sham NPRS score. The orange line represents post- NPRS scores. Participants are along the x axis and NPRS scores are along the y axis. The NPRS ranks pain from 0-10 where 0=no pain and 10= the worst pain imaginable.

CHAPTER 5: Quantitative Sensory profiles of Chemotherapy Induced Peripheral Neuropathy: Are there differences in sensory profiles for neuropathic versus nociceptive pain?

Running Head: Neuropathic pain sensory profiles in CIPN

MY CONTRIBUTION TO THE MANUSCRIPT

The data for this descriptive study came from the physical therapy study. The development of the of physical therapy paper was a joint collaboration between Dr. Barbara Shay, Dr. Marshall Pitz and myself. I completed the literature search, developed the research questions and protocol with guidance, assisted in grant writing, completed ethics applications to both the Health Research Ethics Board and Research Resource Impact Committee. Dr. Pitz, Linda Davidson, and Lori Santoro were vital to recruitment by informing patients of the trial and signing consent to contact forms. I completed recruitment, consented and assessed participants throughout the duration of chemotherapy to the final appointment 6 months post-chemotherapy. I ran the project for the 3 years of data collection. Pascal Lambert analyzed the data. I interpreted the results and prepared the manuscript for publication in a peer reviewed journal.

ABSTRACT

Purpose: To define the sensory phenotypes of taxane induced peripheral neuropathy (TIPN) in a breast cancer population between neuropathic and non-neuropathic symptoms to identify future targets for mechanism-based pain management.

Methods: Participants (n=48) with stage I-III breast cancer were recruited at CancerCare Manitoba. Self-report questionnaires (Numeric Pain Rating Scale (NPRS) and the Disability of the Arm, Shoulder and Hand (DASH)) and Quantitative Sensory Testing (thermal, vibration, and pressure algometry) were used to assess TIPN sensory symptoms. The Self report version of the Leeds Assessment for Neuropathic Symptoms and Signs (S-LANSS) divided the groups into neuropathic and non-neuropathic sensory phenotypes. In total, 5 visits over approximately 8 months duration assessed each participant from pre-chemotherapy to 6 months post-chemotherapy.

Results: 191 nerve assessments, 150 had a S-LANSS <12 defined as 'non-neuropathic' and 41 scored >12, which was defined as 'neuropathic'. NPRS was analyzed based on percentages of those experiencing 1+ pain (graded 1/10 or higher) versus no pain. The neuropathic group had 82.9% of 1+ pain vs 28.7% in the non-neuropathic group (OR 7.49, 95% CI 2.76-20.3, p=0.001). The neuropathic group reported impaired function on the DASH (p=0.002). Heat pain threshold resulted in statistical differences for the left, but not right hand in the neuropathic group (p=0.05).

Conclusion: CIPN and neuropathic pain are difficult to treat. Why some patients with TIPN report severe painful sensory disturbances while others report numbness remains unknown. Participants with neuropathic pain demonstrated significant differences with increased pain and decreased function. Heat pain thresholds were normalized in the

neuropathic group. This may suggest that the neuropathic group retained C-fibre and TRPV1 function.

KEY WORDS: neuropathic pain, mechanism-based pain management, dual nerve disorder, taxane induced peripheral neuropathy (TIPN), chemotherapy induced peripheral neuropathy (CIPN)

INTRODUCTION

Taxane chemotherapy is used by oncologists for many solid tumors including patients with stage I-III breast cancer treated with curative intent. Eighty – 97% of patients exposed to taxane chemotherapy will experience a sensory neuropathy in the hands and/or feet caused by the neurotoxic medication (Kerckhove et al., 2017; Starobova & Vetter, 2017). Persistence of symptoms for many exposed to taxanes can be for months or years post-treatment (Kerckhove et al., 2017; Park et al., 2011; Speck et al., 2013). Neuropathic pain is difficult to treat, and presently there are few effective treatment options specific to chemotherapy induced peripheral neuropathy (CIPN) (Hershman et al., 2014; Park et al., 2011). Duloxetine is the only first line agent with moderate success for CIPN (Hershman et al., 2014; Smith et al., 2013). Unfortunately, side effects including sedation, nausea, constipation and ataxia limit the usefulness of this drug (Moulin et al., 2014). While some patients experience primarily sensory loss (hypoesthesia), others have burning neuropathic pain (hyperalgesia and allodynia), or various combinations of positive and negative sensory profiles that include hypoesthesia, dysesthesia, hyperalgesia and allodynia. Reviews on chemotherapy induced peripheral neuropathy frequently describe all symptoms of the neuropathy (both positive and negative) together (Brewer, Morrison, Dolan, & Fleming, 2016; Grisold, Cavaletti, & Windebank, 2012; Kerckhove et al., 2017; Seretny et al., 2014). There are substantial differences in quality of life for breast cancer survivors between experiencing ‘a little numbness’ and ‘burning pain’; and, it is important to separate and define these two phenotypes. An emerging mechanism-based pain management theory suggests that treatment of neuropathic pain should be specific to the sensory phenotype rather

than the diagnosis. It is theorized that specific pharmacological treatments may respond more appropriately to specific phenotypes (i.e. heat hyperalgesia, cold allodynia or lower pain pressure thresholds). For example, higher heat pain thresholds in patients with post-herpetic neuralgia benefited more from opioids than those with lower heat thresholds (Cruz-Almeida & Fillingim, 2014; Edwards, Haythornthwaite, Tella, Max, & Raja, 2006). A mechanism-based pain management approach recognizes that, at present, it remains unknown which medications work on specific sensory signs. Large multi-centre trials using quantitative sensory testing (QST) have been recommended to identify similar sensory characteristics underlying different causes of neuropathic pain (Attal et al., 2011).

This descriptive study aimed to gain a better understanding of the different sensory phenotypes experienced in taxane induced peripheral neuropathy (TIPN). The goal was to determine whether different sensory characteristics were evident using quantitative sensory testing (QST) in participants with and without neuropathic pain.

Purpose

To define the sensory phenotypes of taxane induced peripheral neuropathy in a breast cancer population. The Self report version of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) was used to define symptoms that were ‘neuropathic’ versus ‘non-neuropathic’ during and after chemotherapy. Using quantitative sensory testing, we sought to improve understanding of neuropathic and non-neuropathic pain profiles in order to identify future targets for mechanism-based pain management in patients with breast cancer.

Hypothesis

It was hypothesized that the S-LANSS questionnaire would identify between group differences in QST measures for neuropathic and non-neuropathic symptom profiles. Specifically, the neuropathic pain group would have lower pain pressure thresholds (central sensitization), lower thermal detection thresholds (improved perception), and increased cold pain thresholds demonstrating hyperalgesia. It was also hypothesized that participants would report higher pain scores and decreased upper extremity function in the neuropathic group.

METHODS

Data Collection

Participants' data was collected as part of a larger physical therapy and nerve health trial evaluating the effects of a home exercise program on upper extremity pain and nerve function. Forty-eight participants completed self-report questionnaires and quantitative sensory testing as part of the trial and were seen for re-assessment of nerve function during and after chemotherapy on 4 occasions over approximately a 7-8 month period. Nerve re-assessments were completed at the Pain Research Laboratory, College of Rehabilitation Sciences, University of Manitoba. Re-assessments occurred 1) midway through chemotherapy 2) end of chemotherapy 3) 3 months post-chemotherapy and 4) 6 months post-chemotherapy. Ethics approval was granted by both the Health Research Ethics Board (H:2014:281) at the University of Manitoba and the Research Resource Impact Committee (RRIC 2014-031) at CancerCare Manitoba.

The Self report version of the Leeds Assessment for Neuropathic Symptoms and Signs (S-LANSS) defined neuropathic pain (Bennett, Smith, Torrance, & Potter, 2005). The scale ranges from 0-19 with a score above 12 indicative of neuropathic pain/symptoms. Studies using the S-LANSS have demonstrated good accuracy and specificity in a cancer population (Hardy, Quinn, Fazekas, Agar, & Currow, 2013; Perez et al., 2015). Participants scores >12 defined the 'neuropathic' group while <12 defined 'non-neuropathic'. Participants with stage I-III breast cancer being treated with taxane chemotherapy, either TC (docetaxel 75mg/m2 and cyclophosphamide x 4) or FECD (5-fluorouracil, epirubicin, cyclophosphamide x3, followed by Docetaxel 100mg/m2 x 3), were included. All quantitative outcome measures, functional measures, and pain questions were specific to assessment of the hands.

Outcome Measures

1) Thermal detection thresholds (warm and cool) and thermal pain thresholds (hot and cold) measure Aδ and C-fibre function and was used to quantify the neuropathy on each assessment. The Neurosensory Analyzer (TSA ll, Medoc, Israel) thermode was attached to the palmer surface of the distal phalanx of the index and middle finger. Temperature is increased or decreased by 0.1 degrees Celsius (°C) increments until the participant presses a button indicating temperature detection thresholds or thermal pain. The temperature immediately returns to baseline (32°C) once the button is pressed. The participant is always in control and is never at risk for tissue damage (temperature limits are set to vary from 0-50 degrees Celsius).

2) The TSAII Vibration Sensory Analyzer module for the Medoc was used to test vibration perception involving Aβ nerve fibres. The palmer distal phalanx of the index finger lightly touched the sensor. Different, random and varying vibration amplitudes (µm) were delivered with the participant responding “yes/no” to sensing the vibration. Vibration perception was selected as it has been suggested to be the first clinical sign of CIPN symptoms (Gutierrez-Gutierrez, Sereno, Miralles, Casado-Saenz, & Gutierrez-Rivas, 2010).

3) Pressure Algometry measured pressure/pain thresholds (Somedic AB, Sweden). The left quadriceps muscle was tested as a measure of central sensitization. Increasing pressure was applied to the left quadriceps until sensation changed from a feeling of pressure to a feeling of pain. The participant pressed a button and the test stopped when pain was perceived. Force in kilopascals (Kpa) was recorded.

4) Numeric Pain Rating Scale (NPRS) is an 11-point scale rating hand CIPN pain (0-10) on each assessment visit. The scale categories range from no pain at all (0) to the worst pain imaginable (10).

5) Disability of the Arm, Shoulder and Hand (DASH) was used to gauge upper/lower limb function. The DASH, a self-reported questionnaire, was chosen because of high test-retest reliability and the responsiveness and construct validity in breast cancer patients over other quality of life measures (Beaton et al., 2001; Harrington, Michener, Kendig, Miale, & George, 2014). The minimal clinically important difference is a change score of 15.

Data Analysis

Outcomes were compared over time between participants with either an S-LANSS score greater than or equal to 12 or below 12 (i.e., S-LANSS was included as a time-varying predictor). Mixed models were used to compare outcomes between groups, to account for repeated measurements and unequal time intervals. Linear mixed models were used to predict continuous outcomes when the assumption of normality was met. Logistic mixed models were used for predicting binary outcomes, and the results were marginalized using the approach by Hedeker (Hedeker, Toit, Demirtas, & Gibbons, 2018), which converts the 'subject-specific' estimates to 'population-averaged' estimates. Residual plots were used to evaluate the assumption of normality and to detect outliers. The assumption of linearity for continuous predictors was evaluated using restricted cubic splines. Analyses were run using R project for statistical computing software version 3.4.1 (R. Development team, 2017) and SAS version 9.4.

RESULTS

A total of 191 participant visits were included in this analysis. Table 1. shows the participant demographics including age, stage, cancer side, surgery, adjuvant treatment, history of nerve entrapment or damage, and loss of shoulder range of motion (ROM) at baseline. Participants had a mean age of 61.5 (range 34-78). Seventeen (35.4%) participants were classified as stage I, 22 (45.8%) in stage II, and 9 (18.8%) as stage III. Nineteen (39.6) participants had right sided breast cancer, 28 (58.3%) had left sided, and 1 (2.1%) had bilateral cancer. Ten (20.8%) participants received

reconstructive surgery, 37 (77.1%) received radiation post-chemotherapy. Thirty (62.5%) participants received FECD and 18 (37.5%) received TC.

Out of 191 nerve assessments, 150 had a S-LANSS <12 defined as 'non-neuropathic' and 41 scored >12, which was defined as 'neuropathic'. Therefore, 21% of participant nerve assessment visits demonstrated neuropathic pain. The remaining 79% either had no complaints of CIPN sensory symptoms or no pain defined as neuropathic associated with CIPN dysesthesias. The DASH score showed statistically significant differences between the groups in that the neuropathic group demonstrated impaired upper limb function (p=0.002). More importantly, the DASH scores mean of 35 (31-46) in the non-neuropathic group versus 51 (41-67) in the neuropathic group meet the minimum clinical important difference (MCID) in change scores indicating that these groups are not only statistically, but also, clinically different (Beaton et al., 2001).

Due to the unequal distribution of pain scores, the 11-point NPRS was analyzed based on percentages of those experiencing pain (NPRS 1 or higher) versus no pain. Using logistic mixed models predicting binary outcomes, participants rating pain was 82.9% in the neuropathic group versus 28.7% in the non-neuropathic group. This was statistically significant and reflects the distinct differences in pain symptoms between the groups (OR 7.49, 95% CI 2.76-20.3, p=0.001) for the hands.

While 21% of nerve assessments indicated neuropathic pain, only 10.4% of participants (n=5) continued to suffer with persistent neuropathic pain at the end of the trial (6-month post-chemotherapy). Descriptive analysis of these participants revealed that 4/5 received FECD, 4/5 had a lumpectomy, 2/5 had a history of nerve entrapment

or damage, 3/5 had limitations in shoulder range of motion (ROM) at baseline and all 5 received radiation.

Heat pain threshold resulted in statistical differences for the left, but not right hand in the neuropathic group (p=0.05). The neuropathic group (left 42.3° C, right 42.5° C) were closer to age matched normative values (41.8 - 42.1° C) than the non-neuropathic group values (left 43.7° C, right 44.1° C) (Gonzalez-Duarte, Lem-Carrillo, & Guerrero-Torres, 2016). All other variables including warm and cool detection, cold pain, vibration sensation, and pain pressure algometry were not significantly different between the groups. Table 2. shows all the mean (SD) and median (Q1-Q3) outcome measures with p-values for the participants divided into neuropathic and non-neuropathic conditions.

DISCUSSION

The S-LANSS is an easy to administer, quick and useful tool to evaluate neuropathic symptoms in a breast cancer population. The S-LANSS clearly delineated neuropathic pain indicating significantly higher pain and impaired upper extremity function between the neuropathic and the non-neuropathic CIPN group. In addition to increased pain and loss of function, severity of CIPN symptoms have been associated with depression, anxiety, and poor sleep quality (Hong, Tian, & Wu, 2014). Increased costs to patients and the healthcare system from CIPN have been quantified at over seventeen thousand US dollars more per year compared to patients without CIPN (Pike, Birnbaum, Muehlenbein, Pohl, & Natale, 2012).

Results of the QST data revealed significant differences in left hand heat pain thresholds with the neuropathic pain group demonstrating lower heat pain thresholds. A potential explanation for these findings surrounds possible preservation of C-fibre and Aδ fibre function. The lower heat pain thresholds in the neuropathic group (left 42.3° C, right 42.5° C) are closer to normative age matched values (41.8 - 42.1° C) in the hand than the non-neuropathic group (left 43.7° C, right 44.1° C). The non-neuropathic group demonstrated slightly higher thresholds than age matched normative data possibly suggesting heat hypoesthesia (Gonzalez-Duarte et al., 2016). Reviews have identified a common feature of CIPN being heat hypoalgesia with cold allodynia as a characteristic of painful CIPN (Han & Smith, 2013; Seretny et al., 2014). Suggested mechanisms for heat hypoesthesia are through the loss of Aδ and C-fibres and transient potential vanilloid 1 (TRPV1) receptors (Han & Smith, 2013). Heat pain thresholds similar to normative age matched values for the neuropathic group may then suggest preservation of these receptors and pathways. Transient receptor potentials channels (TRPs), specifically TRPV1, are important in pain transmission directly through Ca^{2+} signaling and activation of second messengers (Jardin et al., 2017). Given the importance of sensitization and TRPs in pain signaling, a lack of correlation between heat hypoesthesia and the neuropathic pain group may be expected. A second explanation is that a significant finding on only hand may be due to a random effect of assessing multiple variables and not represent preservation of sensory fibres.

Cold allodynia (commonly associated with neuropathic pain) and reduced pain pressure thresholds (suggested to represent central sensitization) demonstrated no significant between group differences. This was surprising and unexpected; however, it

is possible that the mechanisms causing CIPN (microtubule stability at distal axon) do not result in different sensory profiles that are sensitive to QST measurement. Neuropathic pain is thought to be initiated and maintained, at least partly, by the immune system. Microglia and mast cell activation along with the recruitment of astrocytes incite and maintain neuroinflammation (J. Fernandes & Kumar, 2016; V. Fernandes et al., 2018; Lees et al., 2017; Skaper, Facci, Zusso, & Giusti, 2017). Neuroimmune changes may primarily impact higher order processing and interpretation of pain in the central nervous system. The biopsychosocial components of past experience and expectation are thought to play a substantial role in processing, interpretation and response to noxious stimuli.

As expected, the neuropathic group had statistically significant higher reports of pain (NPRS) and decreased function as reported by the DASH. This presentation is often what is witnessed clinically. Significant pain often extending beyond the site of injury, poor function, reduced work and activity levels with disrupted sleep are common features of neuropathic pain.

Large interpersonal variability exists in the location and intensity of neuropathic symptoms. Cumulative dose, schedule, combination therapy, pre-existing risk factors (including diabetes, advanced age, smoking, increased alcohol consumption), increased body mass index (BMI), and genetic predisposition have been used to explain this variability (Cioroiu & Weimer, 2017; Eckhoff, Feddersen, Knoop, Ewertz, & Bergmann, 2015; Kandula et al., 2017; Kus et al., 2016). Our study controlled for some variability by using a single cancer type, single drug, similar dose and schedule, as well as a

consistent time frame for repeat nerve assessments. Other factors such as smoking, body mass index and alcohol consumption was not included in the current study.

Our data revealed that 21% of nerve assessments indicated pain neuropathic in origin. Most of the reports of neuropathic pain were during chemotherapy (n=16). Half of the neuropathic symptoms were transient and 10.4% of participants (n=5) continued to suffer with persistent neuropathic pain at the end of the trial (6-month post-chemotherapy). Of these, 40% (2/5) had a history of nerve entrapment or damage, 60% (3/5) had limitations in shoulder range of motion (ROM) at baseline and all (5/5) received radiation. There is the possibility that scaring from radiation or pre-existing nerve damage may impact the persistence or severity of symptoms.

Pre-existing neuropathy or prior history of nerve injury (including entrapment such as carpal tunnel) has been identified as a potential risk factor for CIPN (Grisold et al., 2012; Seretny et al., 2014; Stubblefield, McNeely, Alfano, & Mayer, 2012). Out of the 5 participants that had persistent neuropathic pain at the end of the trial, 3 began chemotherapy with restricted ROM and 2 had a history of upper extremity nerve injury. This may potentially be important, contributing to a dual nerve disorder. The ‘double crush syndrome’ or ‘dual nerve disorder’, as it is now called, is a hypothesis first identified by Upton and McComas in 1973. It states that ‘axons that have been compressed at one site become especially susceptible to damage at another site’ (Upton & McComas, 1973). It is thought that a minimal amount nerve compression affects axoplasmic flow but is below the threshold for clinical symptoms. A secondary insult further reduces axoplasmic flow resulting in clinical symptoms and denervation. Expert views on the dual nerve disorder theory (Schmid & Coppieters, 2011) agreed

that neurotoxic medication when combined with other nerve disorders might make the nervous system more susceptible to damage. This may be similar to the dual nerve disorders frequently seen in diabetics where the metabolic damage to the peripheral nervous system compounds the effects of entrapment neuropathies (Vinik, Mehrabyan, Colen, & Boulton, 2004).

Unfortunately, this current descriptive study did not find associations in QST to support the mechanism-based approach. The mechanism-based approach focuses primarily on a biomedical explanation. Pain, especially chronic and neuropathic pain is known to have a substantial psychosocial component that needs to be integrated with the biological mechanisms. This current study did not measure psychosocial components of CIPN neuropathic pain (for example; measuring pain catastrophizing, anxiety or fear) and is a clear limitation preventing greater understanding of this neuropathy. Despite this limitation, it is important to understand that different sensory complaints in CIPN do not seem to have distinct sensory profiles as measured by QST with the possible exception of heat pain thresholds.

The S-LANSS can quickly evaluate severe sensory phenotypes of neuropathic pain impacting quality of life and is useful in clinic. An NRPS alone cannot distinguish between neuropathic and other nociceptive pain. The S-LANSS is easy and quick to administer, has good accuracy and specificity in a cancer population (Hardy et al., 2013; Perez et al., 2015), and is a good screening tool to identify potential neuropathic pain from CIPN.

Limitations

This data came from a larger physical therapy study evaluating a home program aiming to improve CIPN symptoms with range of motion and nerve mobility exercises that would also help restore function post-operatively, minimizing a dual nerve disorder in the upper limb. While it is recognized that CIPN is a symmetric, bilateral sensory neuropathy affecting both hands and feet, our study only included the hands. This was for a few reasons. Doubling the time at re-assessment to assess both hands and feet was not feasible with ill participants (midway and end of chemotherapy). We were also concerned with the risk of attrition if the home physical therapy program took too much time to complete. The upper limb was chosen because of the known upper extremity morbidity in this population (Hayes et al., 2012; Kelley & Jull, 1998; Stubblefield et al., 2012). Even so, it is recognized that some symptoms were overlooked by excluding the lower limb. There is also the possibility that the heat pain threshold data was a random association from analysis including multiple comparisons, especially considering statistical significance was not bilateral in both hands. Future studies should use the visual analog scale as a continuous measure in place of the NPRS for improved sensitivity. While the purpose was evaluating specific sensory phenotypes for mechanism-based pain management, the importance of the psychosocial aspects of pain were overlooked that clearly have an impact in pain perception. Finally, QST presents a quantifiable stimulus but with a subjective response. Attention, focus and standardized assessment all impact the validity and reliability of QST. For the purposes of the present study QST provided the most appropriate and descriptive data for quantifying the small fibre sensory neuropathy.

CONCLUSION

Currently, the cause of both CIPN and neuropathic pain are not established. Both CIPN and neuropathic pain conditions are difficult to treat with few effective options. Why some patients with breast cancer treated with chemotherapy report severe painful sensory disturbances while others report a slight amount of numbness remains unknown. It is also unclear whether normal heat thresholds may be part of neuropathic pain symptom profile (suggesting intact C-fibres and TRPV1 receptors that transmit pain). Defining sensory phenotypes of CIPN was not possible in the current study to support mechanism-based pain management. We suspect that the biopsychosocial model of pain processing can better explain the different sensory phenotypes observed in this neuropathy.

REFERENCES

Attal, N., Bouhassira, D., Baron, R., Dostrovsky, J., Dworkin, R. H., Finnerup, N., . . . Treede, R. D. (2011). Assessing symptom profiles in neuropathic pain clinical trials: can it improve outcome? *European journal of pain (London, England), 15*(5), 441-443. doi:10.1016/j.ejpain.2011.03.005; 10.1016/j.ejpain.2011.03.005

Beaton, D. E., Katz, J. N., Fossel, A. H., Wright, J. G., Tarasuk, V., & Bombardier, C. (2001). Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. *Journal of hand therapy : official journal of the American Society of Hand Therapists, 14*(2), 128-146.

Bennett, M. I., Smith, B. H., Torrance, N., & Potter, J. (2005). The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *The journal of pain : official journal of the American Pain Society, 6*(3), 149-158. doi:10.1016/j.jpain.2004.11.007

Brewer, J. R., Morrison, G., Dolan, M. E., & Fleming, G. F. (2016). Chemotherapy-induced peripheral neuropathy: Current status and progress. *Gynecologic oncology, 140*(1), 176-183. doi:10.1016/j.ygyno.2015.11.011 [doi]

Cioroiu, C., & Weimer, L. H. (2017). Update on Chemotherapy-Induced Peripheral Neuropathy. *Current neurology and neuroscience reports, 17*(6), 47-017-0757-0757. doi:10.1007/s11910-017-0757-7 [doi]

Cruz-Almeida, Y., & Fillingim, R. B. (2014). Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain medicine (Malden, Mass.), 15*(1), 61-72. doi:10.1111/pme.12230; 10.1111/pme.12230

Eckhoff, L., Feddersen, S., Knoop, A. S., Ewertz, M., & Bergmann, T. K. (2015). Docetaxel-induced neuropathy: a pharmacogenetic case-control study of 150 women with early-stage breast cancer. *Acta Oncologica (Stockholm, Sweden), 54*(4), 530-537. doi:10.3109/0284186X.2014.969846 [doi]

Edwards, R. R., Haythornthwaite, J. A., Tella, P., Max, M. B., & Raja, S. (2006). Basal heat pain thresholds predict opioid analgesia in patients with postherpetic neuralgia. *Anesthesiology, 104*(6), 1243-1248.

Fernandes, J., & Kumar, S. (2016). Effect of lower limb closed kinematic chain exercises on balance in patients with chemotherapy-induced peripheral neuropathy: a pilot study. *International journal of rehabilitation research.Internationale Zeitschrift fur Rehabilitationsforschung.Revue internationale de recherches de readaptation, 39*(4), 368-371. doi:10.1097/MRR.0000000000000196 [doi]

Fernandes, V., Sharma, D., Vaidya, S., P, A. S., Guan, Y., Kalia, K., & Tiwari, V. (2018). Cellular and molecular mechanisms driving neuropathic pain: recent advancements and challenges. *Expert Opin Ther Targets, 22*(2), 131-142. doi:10.1080/14728222.2018.1420781

Gonzalez-Duarte, A., Lem-Carrillo, M., & Guerrero-Torres, L. (2016). Normative values of quantitative sensory testing in Hispanic Latino population. *Brain Behav, 6*(7), e00466. doi:10.1002/brb3.466

Grisold, W., Cavaletti, G., & Windebank, A. J. (2012). Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro-oncology, 14 Suppl 4*, iv45-54. doi:10.1093/neuonc/nos203; 10.1093/neuonc/nos203

Gutierrez-Gutierrez, G., Sereno, M., Miralles, A., Casado-Saenz, E., & Gutierrez-Rivas, E. (2010). Chemotherapy-induced peripheral neuropathy: clinical features, diagnosis, prevention and treatment strategies. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico, 12*(2), 81-91. doi:10.1007/S12094-010-0474-z; 10.1007/S12094-010-0474-z

Han, Y., & Smith, M. T. (2013). Pathobiology of cancer chemotherapy-induced peripheral neuropathy (CIPN). *Frontiers in pharmacology, 4*, 156. doi:10.3389/fphar.2013.00156 [doi]

Hardy, J., Quinn, S., Fazekas, B., Agar, M., & Currow, D. (2013). Can the LANSS scale be used to classify pain in chronic cancer pain trials? *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 21*(12), 3387-3391. doi:10.1007/s00520-013-1921-5 [doi]

Harrington, S., Michener, L. A., Kendig, T., Miale, S., & George, S. Z. (2014). Patient-reported upper extremity outcome measures used in breast cancer survivors: a systematic review. *Archives of Physical Medicine and Rehabilitation, 95*(1), 153-162. doi:10.1016/j.apmr.2013.07.022 [doi]

Hayes, S. C., Johansson, K., Stout, N. L., Prosnitz, R., Armer, J. M., Gabram, S., & Schmitz, K. H. (2012). Upper-body morbidity after breast cancer: incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. *Cancer, 118*(8 Suppl), 2237-2249. doi:10.1002/cncr.27467; 10.1002/cncr.27467

Hedeker, D., Toit, S. H. C. d., Demirtas, H., & Gibbons, R. D. (2018). A note on marginalization of regression parameters from mixed models of binary outcomes. *Biometrics, 74*(1), 354-361. doi:doi:10.1111/biom.12707

Hershman, D. L., Lacchetti, C., Dworkin, R. H., Lavoie Smith, E. M., Bleeker, J., Cavaletti, G., . . . American Society of Clinical, O. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 32*(18), 1941-1967. doi:10.1200/JCO.2013.54.0914; 10.1200/JCO.2013.54.0914

Hong, J. S., Tian, J., & Wu, L. H. (2014). The influence of chemotherapy-induced neurotoxicity on psychological distress and sleep disturbance in cancer patients. *Current oncology (Toronto, Ont.), 21*(4), 174-180. doi:10.3747/co.21.1984 [doi]

Jardin, I., Lopez, J. J., Diez, R., Sanchez-Collado, J., Cantonero, C., Albarran, L., . . . Rosado, J. A. (2017). TRPs in Pain Sensation. *Front Physiol, 8*, 392. doi:10.3389/fphys.2017.00392

Kandula, T., Farrar, M. A., Kiernan, M. C., Krishnan, A. V., Goldstein, D., Horvath, L., . . . Park, S. B. (2017). Neurophysiological and clinical outcomes in chemotherapy-induced neuropathy in cancer. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 128*(7), 1166-1175. doi:S1388-2457(17)30155-4 [pii]

Kelley, S., & Jull, G. (1998). Breast surgery and neural tissue mechanosensitivity. *The Australian journal of physiotherapy, 44*(1), 31-37.

Kerckhove, N., Collin, A., Conde, S., Chaleteix, C., Pezet, D., & Balayssac, D. (2017). Long-Term Effects, Pathophysiological Mechanisms, and Risk Factors of Chemotherapy-Induced Peripheral Neuropathies: A Comprehensive Literature Review. *Frontiers in pharmacology, 8*, 86. doi:10.3389/fphar.2017.00086 [doi]

Kus, T., Aktas, G., Kalender, M. E., Sevinc, A., Kul, S., Suner, A., . . . Camci, C. (2016). Taxane-induced peripheral sensorial neuropathy in cancer patients is associated with duration of diabetes mellitus: a single-center retrospective study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 24*(3), 1175-1179. doi:10.1007/s00520-015-2898-z [doi]

Lees, J. G., Makker, P. G., Tonkin, R. S., Abdulla, M., Park, S. B., Goldstein, D., & Moalem-Taylor, G. (2017). Immune-mediated processes implicated in chemotherapy-induced peripheral neuropathy. *European journal of cancer (Oxford, England : 1990), 73*, 22-29. doi:S0959-8049(16)33095-7 [pii]

Moulin, D., Boulanger, A., Clark, A. J., Clarke, H., Dao, T., Finley, G. A., . . . Williamson, O. D. (2014). Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain research & management : the journal of the Canadian Pain Society = journal de la societe canadienne pour le traitement de la douleur, 19*(6), 328-335.

Park, S. B., Lin, C. S., Krishnan, A. V., Friedlander, M. L., Lewis, C. R., & Kiernan, M. C. (2011). Early, progressive, and sustained dysfunction of sensory axons underlies paclitaxel-induced neuropathy. *Muscle & nerve, 43*(3), 367-374. doi:10.1002/mus.21874; 10.1002/mus.21874

Perez, C., Sanchez-Martinez, N., Ballesteros, A., Blanco, T., Collazo, A., Gonzalez, F., & Villoria, J. (2015). Prevalence of pain and relative diagnostic performance of screening tools for neuropathic pain in cancer patients: A cross-sectional study. *European journal of pain (London, England), 19*(6), 752-761. doi:10.1002/ejp.598 [doi]

Pike, C. T., Birnbaum, H. G., Muehlenbein, C. E., Pohl, G. M., & Natale, R. B. (2012). Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and nonsmall cell lung cancer. *Chemotherapy research and practice, 2012*, 913848. doi:10.1155/2012/913848 [doi]

R: A Language and Envoironment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN3-900051-07-0, URL http://www.R-project.org.

Schmid, A. B., & Coppieters, M. W. (2011). The double crush syndrome revisited--a Delphi study to reveal current expert views on mechanisms underlying dual nerve disorders. *Manual therapy, 16*(6), 557-562. doi:10.1016/j.math.2011.05.005 [doi]

Seretny, M., Currie, G. L., Sena, E. S., Ramnarine, S., Grant, R., MacLeod, M. R., . . . Fallon, M. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain, 155*(12), 2461-2470. doi:10.1016/j.pain.2014.09.020; 10.1016/j.pain.2014.09.020

Skaper, S. D., Facci, L., Zusso, M., & Giusti, P. (2017). Neuroinflammation, Mast Cells, and Glia: Dangerous Liaisons. *Neuroscientist, 23*(5), 478-498. doi:10.1177/1073858416687249

Smith, E. M., Pang, H., Cirrincione, C., Fleishman, S., Paskett, E. D., Ahles, T., . . . Alliance for Clinical Trials in, O. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a

randomized clinical trial. *Jama, 309*(13), 1359-1367. doi:10.1001/jama.2013.2813; 10.1001/jama.2013.2813

Speck, R. M., Sammel, M. D., Farrar, J. T., Hennessy, S., Mao, J. J., Stineman, M. G., & DeMichele, A. (2013). Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in nonmetastatic breast cancer. *Journal of oncology practice / American Society of Clinical Oncology, 9*(5), e234-240. doi:10.1200/JOP.2012.000863; 10.1200/JOP.2012.000863

Starobova, H., & Vetter, I. (2017). Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. *Frontiers in molecular neuroscience, 10*, 174. doi:10.3389/fnmol.2017.00174 [doi]

Stubblefield, M. D., McNeely, M. L., Alfano, C. M., & Mayer, D. K. (2012). A prospective surveillance model for physical rehabilitation of women with breast cancer: chemotherapy-induced peripheral neuropathy. *Cancer, 118*(8 Suppl), 2250-2260. doi:10.1002/cncr.27463; 10.1002/cncr.27463

Upton, A. R., & McComas, A. J. (1973). The double crush in nerve entrapment syndromes. *Lancet (London, England), 2*(7825), 359-362. doi:S0140-6736(73)93196-6 [pii]

Vinik, A., Mehrabyan, A., Colen, L., & Boulton, A. (2004). Focal entrapment neuropathies in diabetes. *Diabetes care, 27*(7), 1783-1788. doi:27/7/1783 [pii]

TABLE 1. DEMOGRAPHICS

Participant Demographics	
Age mean (SD)	61.5 (23.33)
Stage n (%)	
I	17(35.4)
II	22(45.8)
III	9(18.8)
Cancer Side (n(%)	
Right	19(39.6)
Left	28(58.3)
Bilateral	1(2.1)
Surgery n(%)	
Lumpectomy	27(56.2)
Single Mastectomy	15(31.3)
Bilateral Mastectomy	6(12.5)
Reconstruction	10(20.8)
Radiation (n (%)	37(77.1)
Docetaxel n(%)	
FECD (6 rounds/3 taxane)	30(62.5)
TC (4 rounds/all include taxane)	18(37.5)
Loss of range of motion - shoulder n(%)	13 (27.1)
History of upper extremity nerve problems n(%)	13 (27.1)

TABLE 2. NEUROPATHIC AND NON-NEUROPATHIC SYMPTOM PROFILES

	Neuropathic	Non-neurpathic	p value
Warm Detection mean(SD)			
Left	35.7 (2.38)	35.3 (2.22)	p=0.27
Right	36.3 (1.60)	35.9 (1.90)	p=0.65
Cool Detection mean(SD)			
Left	29.8 (1.69)	30.0 (1.67)	p=0.35
Right	29.3 (1.94)	29.3 (2.86)	p=0.35
Hot Pain Thresholds mean(SD)			
Left	42.3 (3.33)	43.7 (3.51)	p=0.17
Right	42.5 (2.93)	44.1 (3.11)	p=0.05*
Cold Pain Thresholds mean(SD)			
Left	16.8 (9.19)	14.2 (8.97)	p=0.41
Right	16.5 (8.79)	13.9 (9.00)	p=0.46
Vibration median(Q1-Q3)			
Left	0.14 (0.04-0.24)	0.14 (0.04-0.34)	p=0.38
Right	0.23 (0.13-0.49)	0.23(0.13-0.41)	p=0.76
Pressure mean (SD)	752 (315)	843 (348)	p=0.52
NPRS n (%)			
No Pain	7 (17.1)	107 (71.3)	
Pain 1+	34 (82.9)	43(28.7)	p=0.001*
DASH median (Q1-Q3)	51 (41-67)	35 (31-46)	p=0.002*

CHAPTER 6: Exercise may provide Neuroprotection from Chemotherapy Induced Peripheral Neuropathy

Running Head: Neuroprotection from CIPN with exercise

MY CONTRIBUTION TO THE MANUSCRIPT

The data for this descriptive study came from the physical therapy study. Development of the of physical therapy paper was a joint collaboration between Dr. Barbara Shay, Dr. Marshall Pitz and myself. I completed the literature search, developed the research questions and protocol with guidance, assisted in grant writing, completed ethics applications to both the Health Research Ethics Board and Research Resource Impact Committee. Dr. Pitz, Linda Davidson, and Lori Santoro were vital to recruitment by informing patients of the trial and signing consent to contact forms. I completed recruitment, consented and assessed participants throughout the duration of chemotherapy to the final appointment 6 months post-chemotherapy. I ran the project for the 3 years of data collection. Pascal Lambert analyzed the data. I interpreted the results and prepared the manuscript for publication in a peer reviewed journal.

ABSTRACT

Purpose: To explore the theory and observed correlation that exercise may provide neuroprotection from chemotherapy induced peripheral neuropathy

Methods: Participants' (n=48) data from a breast cancer and physical therapy trial was analyzed grouping 'active' (exercise >4 times/week) and 'less active' participants. Baseline quantitative sensory testing (QST) was collected prior to adjuvant taxane chemotherapy for stage I-III. Nerve reassessments for QST were mid chemotherapy, post chemotherapy, 3 months post chemotherapy, and 6 months post chemotherapy. QST data included warm and cool detection thresholds, hot and cold pain thresholds and vibration perception.

Results: the 'active' group revealed significantly improved vibration scores (Left index p=0.001, Right index p=0.001) and a decrease in heat pain thresholds to normal levels bilaterally to the hands (Left index p=0.021, Right Index p=0.039). Warm and cool detection and cold pain showed no significant change.

Conclusion: This research further supports the theory that exercise may provide neuroprotection for CIPN. Women who engage in regular exercise on most days have bilateral improved vibration sense (Aβ fibres) and normal heat pain thresholds (Aδ and C-fibres) compared to more sedentary women during and after chemotherapy.

KEY WORDS: exercise, neuroprotection, chemotherapy induced peripheral neuropathy (CIPN), breast cancer, taxane, quantitative sensory testing (QST)

INTRODUCTION

There is a strong relationship between the benefits of exercise and health in what appears to be a dose-dependent manner (Warburton, Katzmarzyk, Rhodes, & Shephard, 2007). A review of evidence-informed guidelines for Canadians identifies that, if all Canadians followed current guidelines (30-40 minutes of moderate intensity exercise on most days), deaths could be reduced by 20% for colon cancer and 14% for breast cancer (Katzmarzyk & Ardern, 2004; Warburton et al., 2007). Despite this, cancer specific population estimates reveal that fewer than 22% are active (Courneya, Katzmarzyk, & Bacon, 2008; Rogers, Courneya, Verhulst, Markwell, & McAuley, 2008).

In addition to correlations between exercise and survival, further correlations between exercise and improvements in peripheral neuropathy symptoms have been documented. A long-term follow up study on peripheral neuropathy risk factors in breast cancer survivors found an association that exercise of at least 30 minutes on most days was associated with lower risk (12%) of peripheral neuropathy (Mustafa Ali, Moeller, Rybicki, & Moore, 2017). Exercise has also been shown to improve symptoms of CIPN on quality of life (QOL) measures (Streckmann, Kneis, et al., 2014; Streckmann, Zopf, et al., 2014; Wonders et al., 2013). A recent multi-center RCT found a six week progressive walking and resistance program reduced CIPN symptoms as measured by self-report questionnaires for numbness/tingling and hotness/coldness (Kleckner et al., 2018). These studies in addition to epidemiological correlations led us to hypothesize that engaging in exercise throughout chemotherapy was potentially neuroprotective and would preserve Aβ, Aδ and C-fibre function as measured by quantitative sensory testing (QST). As part of a larger physical therapy and CIPN study, we collected data for

analysis on patients who regularly exercised (active group) during and after chemotherapy compared to those that were more sedentary by comparison (less active group).

Purpose

To compare quantitative sensory testing (QST) data between participants who reported engaging in a moderate amount of exercise (reported exercise >4 times per week on 3/4 or more re-assessment visits) to those who were less active throughout breast cancer treatment. This was to evaluate whether participants who regularly exercise may correlate to improved sensory function as measured by QST, suggesting a possible neuroprotective effect.

METHODS

Participants

Participants' data was collected as part of a larger physical therapy and nerve health trial evaluating the effects of a home exercise program on upper extremity pain and nerve function. Forty-eight participants with stage I-III breast cancer being treated with adjuvant taxane chemotherapy, either TC (docetaxel 75mg/m2 and cyclophosphamide x 4) or FECD (5-fluorouracil, epirubicin, cyclophosphamide x3, followed by Docetaxel 100mg/m2 x 3) were included (Jones et al., 2009; Roche et al., 2006; Swain et al., 2013). Nerve assessments on the hands used quantitative sensory testing (QST) to define the small fibre neuropathy. The Pain Research Laboratory (PRL) at the College of Rehabilitation Sciences, University of Manitoba collected the QST

data. Re-assessments occurred 1) midway through chemotherapy 2) end of chemotherapy 3) 3 months post-chemotherapy and 4) 6 months post-chemotherapy. Ethics approval was granted by both the Health Research Ethics Board (H:2014:281) at the University of Manitoba and the Research Resource Impact Committee (RRIC 2014-031) at CancerCare Manitoba.

Measuring Activity

Participants were asked about their level of exercise per week at each assessment visit. Participants were considered active if they engaged in any form of activity at least 4 times a week beyond activities of daily living such as walking to the bus or walking the dog around the block. Types of activities that participants reported included cycling, running, yoga, swimming, Zumba, dance classes, and tennis. Walking was included if it was at least 30 minutes at a moderate pace. It was assumed there would be a decline in activity levels during and right after chemotherapy. 'Active' participants were defined as reporting physical activity on 3/4 or more reassessments versus 'less active' defined as exercising on 2/4 reassessments or less.

Outcome Measures

<u>QST</u>

1) Thermal detection threshold (Neurosensory Analyzer TSA ll, Medoc, Israel) was used for thermal detection (warm and cool) and thermal pain thresholds (hot and cold). As discussed in a previous chapter, the TSAII measures Aδ and C-fibre function and was used to quantify nerve function. The protocol attached the thermode to the palmer

surface of the distal phalanx (tips of fingers) of the index and middle finger. Temperature is increased or decreased by 0.1-degree Celsius increments until the patient presses a button indicating temperature detection or thermal pain. The patient is always in control and is never at risk for tissue damage (temperature limits are set to vary only from 0-50 degrees Celsius).

2) The TSAII Vibration Sensory Analyzer module for the Medoc was used to test vibration perception involving Aβ nerve fibres. As discussed in a previous chapter, the palmer distal phalanx of the index finger lightly touched the sensor. Different, random and varying vibration amplitudes (µm) were delivered with the participant responding "yes/no" to sensing the vibration. Vibration perception was selected as it has been suggested to be the first clinical sign of CIPN symptoms (Gutierrez-Gutierrez, Sereno, Miralles, Casado-Saenz, & Gutierrez-Rivas, 2010).

Data Analysis

To account for repeated measurements and unequal time intervals mixed models were used to compare outcomes for the effect of exercise. Linear mixed models were used to predict continuous outcomes when the assumption of normality was met. Residual plots were used to evaluate the assumption of normality and to detect outliers. The assumption of linearity for continuous predictors was evaluated using restricted cubic splines. Analyses were run using the R project for statistical computing software version 3.4.1. (R. Development team, 2017) and SAS 9.4.

RESULTS

A total of 191 participant visits were included in this analysis. Less active participants made up 131/191 visits, while active participants had 60/191 visits. Table 1. shows the participant demographics including age, stage, cancer side, surgery, adjuvant treatment. Participants mean age was 61.5 (range 34-78). Seventeen (35.4%) participants were classified as stage I, 22 (45.8%) in stage II, and 9 (18.8%) as stage III. Nineteen (39.6) participants had right sided breast cancer, 28 (58.3%) had left sided, and 1 (2.1%) had bilateral cancer. Ten (20.8%) participants received reconstructive surgery, 37 (77.1%) received radiation post-chemotherapy. Thirty (62.5%) participants received FECD and 18 (37.5%) received TC.

The exercise analysis revealed significantly better vibration scores (Left index p=0.001, Right index p=0.001) and a decrease in heat pain thresholds to normal levels bilaterally in the hands (Left index p=0.021, Right Index p=0.039) for those considered ‘active’. Warm and cool detection and cold pain thresholds showed no significant difference between the groups. Table 2. shows the outcome variables grouped by ‘active’ and ‘less active’.

DISCUSSION

This current study revealed that women who remained active during and after chemotherapy had significantly improved vibration sense and reported hot pain thresholds at levels equal to age matched normative values (Gonzalez-Duarte, Lem-Carrillo, & Guerrero-Torres, 2016).

As the significant improvements were bilateral (left and right hand) this strengthens the association and decreases the possibility of a random association. Improved vibration perception suggests a correlation between exercise and preservation of Aβ fibres and Pacinian corpuscles that transmit this sensory perception. Normal heat pain thresholds bilaterally further suggest preservation of Aδ and C-fibres and TRPV1 receptors. Age matched (41-60 years) normative hand heat pain thresholds according to Gonalez-Duarte and others (41.8 - 42.1 C°) is similar to the 'active' group (left 41.8, right 42.5) while the 'less active' group had elevated thresholds (left 44.1, right 44.4). Heat pain thresholds results in the 'less active' group may be due to thermal hypoesthesia from the loss of thermal receptors and/or free nerve endings responsible for transmitting thermal pain. A secondary explanation is the possibility that the 'less active' group had higher pain thresholds (higher pain tolerance) without hypoesthesia.

Exercise is thought to improve pain and sensory nerve function through increasing anti-inflammatory cascades, decreasing pro-inflammatory cytokines, altering activation of glial cells that may prevent neuropathic pain, upregulation of various neurotrophic factors, and expression of proteins including neurotrophin-3 (NT-3) and brain derived neurotrophic factor (BDNF) and heat shock protein-72 (HSP-72) involved in nerve repair and regeneration (Cooper, Kluding, & Wright, 2016; Dobson, McMillan, & Li, 2014; Schmidt, 2014).

The mechanisms of how exercise impacts nerve health in CIPN remain unclear. It is possible that women able to exercise throughout chemotherapy are healthier to begin with, have fewer side effects from treatment, or have other biological mechanisms (hormonal, insulin), or genetic or epi-genetic mechanisms that may be responsible for

the benefit of exercise (Eckhoff, Feddersen, Knoop, Ewertz, & Bergmann, 2015; McTiernan, 2008; Zimmer et al., 2015).

Moderate intensity exercise improves physical health, musculoskeletal fitness and positive mental health (including reduced rates of both depression and anxiety) that greatly impact quality of life (Warburton et al., 2007). Improved survival has been correlated to women that exercise the equivalent of walking 3-5 hours (9 metabolic equivalents METS) or more per week and adhered to a healthy lifestyle (Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005; Pierce et al., 2007). Possible explanations for improved physical health with exercise include lower serum concentrations of sex hormones, improved insulin sensitivity, reduction in systemic inflammation, and improved immune function (McTiernan, 2008).

Despite well-known improvements in cancer survival, quality of life, function and treatment-related side effects, physical activity levels are diminished and do not return to baseline even one year after a breast cancer diagnosis (Baumann et al., 2013; Devoogdt et al., 2010). A prospective breast cancer study (n=267) measuring physical activity confirmed that physical activity declines significantly post-operatively. Follow up at one year found that these women had not returned to their pre-operative physical activity levels (Devoogdt et al., 2010).

Many factors must be considered when prescribing exercise during chemotherapy to encourage compliance. This includes exercise type and duration, social, cognitive, demographic, environmental and medical variables (Courneya, McKenzie, et al., 2008; Rogers et al., 2008). Specifics of barriers to exercise that patients report include treatment side effects, time constraints and fatigue. The barriers

reported are often the symptoms that can be improved with exercise and cancer patients may not be fully aware of the impact exercise can have in improving quality of life (Blaney, Lowe-Strong, Rankin-Watt, Campbell, & Gracey, 2013; Clifford et al., 2018).

Exercise throughout chemotherapy should be encouraged for patients to improve survival, prevent recurrence, improve quality of life, and possibly provide neuroprotection from neurotoxic chemotherapy.

Limitations

The active and less active groups were a sub-group analysis from another trail assessing the impact of physical therapy. These groups were not randomized and the association between sensory preservation and exercise remains to be tested in phase III trials. Measuring sensory function with QST has some drawbacks. While the stimulus is objective, the response is subjective. Focus, attention, standardized protocol in wording all are important variables that can affect the response time and results. There is also the possibility that statistical differences observed were the result of a random effect from assessing multiple variables. However, because bilateral differences in vibration and heat pain thresholds were detected, this supports the correlation between exercise and neuroprotection. We did not monitor exercise as far as keeping a diary or quantifying in a way that would determine metabolic equivalents. This would have been useful and should be collected in future trials. We recognize that the retrospective participant reports of activity may not be an accurate measure. Future trials should

incorporate accelerometry or pedometer data that would provide more objective and quantifiable exercise data.

CONCLUSION

Physical activity during and after medical treatment for cancer is generally encouraged. Physical activity helps maintain and improve cardiovascular fitness, muscle strength, balance, flexibility and range of motion, reduces symptoms of fatigue, depression, and generally improves quality of life (Baumann et al., 2013; Hayes et al., 2012; Streckmann, Kneis, et al., 2014; Streckmann, Zopf, et al., 2014). This research supports the theory that exercise may additionally provide neuroprotection from CIPN. Women who engage in exercise on most days had improved vibration sense (Aβ fibres) and normal heat pain thresholds bilaterally (Aδ and C-fibres) compared to more sedentary women during and after chemotherapy.

REFERENCES

Baumann, F. T., Bloch, W., Weissen, A., Brockhaus, M., Beulertz, J., Zimmer, P., . . . Zopf, E. M. (2013). Physical Activity in Breast Cancer Patients during Medical Treatment and in the Aftercare - a Review. *Breast care (Basel, Switzerland), 8*(5), 330-334. doi:10.1159/000356172 [doi]

Beaton, D. E., Katz, J. N., Fossel, A. H., Wright, J. G., Tarasuk, V., & Bombardier, C. (2001). Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. *Journal of hand therapy : official journal of the American Society of Hand Therapists, 14*(2), 128-146.

Bennett, M. I., Smith, B. H., Torrance, N., & Potter, J. (2005). The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *The journal of pain : official journal of the American Pain Society, 6*(3), 149-158. doi:10.1016/j.jpain.2004.11.007

Blaney, J. M., Lowe-Strong, A., Rankin-Watt, J., Campbell, A., & Gracey, J. H. (2013). Cancer survivors' exercise barriers, facilitators and preferences in the context of fatigue, quality of life and physical activity participation: a questionnaire-survey. *Psychooncology, 22*(1), 186-194. doi:10.1002/pon.2072

Clifford, B. K., Mizrahi, D., Sandler, C. X., Barry, B. K., Simar, D., Wakefield, C. E., & Goldstein, D. (2018). Barriers and facilitators of exercise experienced by cancer survivors: a mixed methods systematic review. *Support Care Cancer, 26*(3), 685-700. doi:10.1007/s00520-017-3964-5

Cooper, M. A., Kluding, P. M., & Wright, D. E. (2016). Emerging Relationships between Exercise, Sensory Nerves, and Neuropathic Pain. *Frontiers in neuroscience, 10*, 372. doi:10.3389/fnins.2016.00372 [doi]

Courneya, K. S., Katzmarzyk, P. T., & Bacon, E. (2008). Physical activity and obesity in Canadian cancer survivors: population-based estimates from the 2005 Canadian Community Health Survey. *Cancer, 112*(11), 2475-2482. doi:10.1002/cncr.23455

Courneya, K. S., McKenzie, D. C., Mackey, J. R., Gelmon, K., Reid, R. D., Friedenreich, C. M., . . . Segal, R. J. (2008). Moderators of the effects of exercise training in breast cancer patients receiving chemotherapy: a randomized controlled trial. *Cancer, 112*(8), 1845-1853. doi:10.1002/cncr.23379

Devoogdt, N., Van Kampen, M., Geraerts, I., Coremans, T., Fieuws, S., Lefevre, J., . . . Christiaens, M. R. (2010). Physical activity levels after treatment for breast cancer: one-year follow-up. *Breast cancer research and treatment, 123*(2), 417-425. doi:10.1007/s10549-010-0997-6 [doi]

Dobson, J. L., McMillan, J., & Li, L. (2014). Benefits of exercise intervention in reducing neuropathic pain. *Front Cell Neurosci, 8*, 102. doi:10.3389/fncel.2014.00102

Eckhoff, L., Feddersen, S., Knoop, A. S., Ewertz, M., & Bergmann, T. K. (2015). Docetaxel-induced neuropathy: a pharmacogenetic case-control study of 150 women with early-stage breast cancer. *Acta Oncologica (Stockholm, Sweden), 54*(4), 530-537. doi:10.3109/0284186X.2014.969846 [doi]

Gonzalez-Duarte, A., Lem-Carrillo, M., & Guerrero-Torres, L. (2016). Normative values of quantitative sensory testing in Hispanic Latino population. *Brain Behav, 6*(7), e00466. doi:10.1002/brb3.466

Gutierrez-Gutierrez, G., Sereno, M., Miralles, A., Casado-Saenz, E., & Gutierrez-Rivas, E. (2010). Chemotherapy-induced peripheral neuropathy: clinical features, diagnosis, prevention and treatment strategies. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico, 12*(2), 81-91. doi:10.1007/S12094-010-0474-z; 10.1007/S12094-010-0474-z

Hardy, J., Quinn, S., Fazekas, B., Agar, M., & Currow, D. (2013). Can the LANSS scale be used to classify pain in chronic cancer pain trials? *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 21*(12), 3387-3391. doi:10.1007/s00520-013-1921-5 [doi]

Harrington, S., Michener, L. A., Kendig, T., Miale, S., & George, S. Z. (2014). Patient-reported upper extremity outcome measures used in breast cancer survivors: a systematic review. *Archives of Physical Medicine and Rehabilitation, 95*(1), 153-162. doi:10.1016/j.apmr.2013.07.022 [doi]

Hayes, S. C., Johansson, K., Stout, N. L., Prosnitz, R., Armer, J. M., Gabram, S., & Schmitz, K. H. (2012). Upper-body morbidity after breast cancer: incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. *Cancer, 118*(8 Suppl), 2237-2249. doi:10.1002/cncr.27467; 10.1002/cncr.27467

Hedeker, D., Toit, S. H. C. d., Demirtas, H., & Gibbons, R. D. (2018). A note on marginalization of regression parameters from mixed models of binary outcomes. *Biometrics, 74*(1), 354-361. doi:doi:10.1111/biom.12707

Holmes, M. D., Chen, W. Y., Feskanich, D., Kroenke, C. H., & Colditz, G. A. (2005). Physical activity and survival after breast cancer diagnosis. *Jama, 293*(20), 2479-2486. doi:10.1001/jama.293.20.2479

Jones, S., Holmes, F. A., O'Shaughnessy, J., Blum, J. L., Vukelja, S. J., McIntyre, K. J., . . . Savin, M. A. (2009). Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 27*(8), 1177-1183. doi:10.1200/JCO.2008.18.4028; 10.1200/JCO.2008.18.4028

Katzmarzyk, P. T., & Ardern, C. I. (2004). Overweight and obesity mortality trends in Canada, 1985-2000. *Canadian journal of public health = Revue canadienne de sante publique, 95*(1), 16-20.

Kleckner, I. R., Kamen, C., Gewandter, J. S., Mohile, N. A., Heckler, C. E., Culakova, E., . . . Mustian, K. M. (2018). Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. *Support Care Cancer, 26*(4), 1019-1028. doi:10.1007/s00520-017-4013-0

McTiernan, A. (2008). Mechanisms linking physical activity with cancer. *Nature reviews.Cancer, 8*(3), 205-211. doi:10.1038/nrc2325 [doi]

Mustafa Ali, M., Moeller, M., Rybicki, L., & Moore, H. C. F. (2017). Long-term peripheral neuropathy symptoms in breast cancer survivors. *Breast cancer research and treatment*. doi:10.1007/s10549-017-4437-8 [doi]

Perez, C., Sanchez-Martinez, N., Ballesteros, A., Blanco, T., Collazo, A., Gonzalez, F., & Villoria, J. (2015). Prevalence of pain and relative diagnostic performance of screening tools for neuropathic pain in cancer patients: A cross-sectional study. *European journal of pain (London, England), 19*(6), 752-761. doi:10.1002/ejp.598 [doi]

Pierce, J. P., Stefanick, M. L., Flatt, S. W., Natarajan, L., Sternfeld, B., Madlensky, L., . . . Rock, C. L. (2007). Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. *J Clin Oncol, 25*(17), 2345-2351. doi:10.1200/jco.2006.08.6819

R: A Language and Environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN3-900051-07-0, URL http://www.R-Project.org.

Roche, H., Fumoleau, P., Spielmann, M., Canon, J. L., Delozier, T., Serin, D., . . . Asselain, B. (2006). Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 24*(36), 5664-5671. doi:10.1200/JCO.2006.07.3916

Rogers, L. Q., Courneya, K. S., Verhulst, S., Markwell, S. J., & McAuley, E. (2008). Factors associated with exercise counseling and program preferences among breast cancer survivors. *J Phys Act Health, 5*(5), 688-705.

Schmidt, B. L. (2014). The neurobiology of cancer pain. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry, 20*(5), 546-562. doi:10.1177/1073858414525828; 10.1177/1073858414525828

Streckmann, F., Kneis, S., Leifert, J. A., Baumann, F. T., Kleber, M., Ihorst, G., . . . Bertz, H. (2014). Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Annals of oncology : official journal of the European Society for Medical Oncology, 25*(2), 493-499. doi:10.1093/annonc/mdt568 [doi]

Streckmann, F., Zopf, E. M., Lehmann, H. C., May, K., Rizza, J., Zimmer, P., . . . Baumann, F. T. (2014). Exercise intervention studies in patients with peripheral neuropathy: a systematic review. *Sports medicine (Auckland, N.Z.), 44*(9), 1289-1304. doi:10.1007/s40279-014-0207-5 [doi]

Swain, S. M., Tang, G., Geyer, C. E., Jr., Rastogi, P., Atkins, J. N., Donnellan, P. P., . . . Wolmark, N. (2013). Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31*(26), 3197-3204. doi:10.1200/JCO.2012.48.1275; 10.1200/JCO.2012.48.1275

Warburton, D. E., Katzmarzyk, P. T., Rhodes, R. E., & Shephard, R. J. (2007). Evidence-informed physical activity guidelines for Canadian adults. *Canadian journal of public health = Revue canadienne de sante publique, 98 Suppl 2*, S16-68.

Wonders, K. Y., Whisler, G., Loy, H., Holt, B., Bohachek, K., & Wise, R. (2013). Ten Weeks of Home-Based Exercise Attenuates Symptoms of Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer Patients. *Health psychology research, 1*(3), e28. doi:10.4081/hpr.2013.e28 [doi]

Zimmer, P., Bloch, W., Schenk, A., Zopf, E. M., Hildebrandt, U., Streckmann, F., . . . Baumann, F. (2015). Exercise-induced Natural Killer Cell Activation is Driven by Epigenetic

Modifications. *International Journal of Sports Medicine, 36*(6), 510-515. doi:10.1055/s-0034-1398531 [doi]

TABLE 1. Demographics

Participant Demographics	
Age mean (SD)	61.5 (23.33)
Stage n (%)	
I	17(35.4)
II	22(45.8)
III	9(18.8)
Cancer Side (n(%)	
Right	19(39.6)
Left	28(58.3)
Bilateral	1(2.1)
Surgery n(%)	
Lumpectomy	27(56.2)
Single Mastectomy	15(31.3)
Bilateral Mastectomy	6(12.5)
Reconstruction	10(20.8)
Radiation (n (%)	37(77.1)
Docetaxel n(%)	
FECD (6 rounds/3 taxane)	30(62.5)
TC (4 rounds/all include taxane)	18(37.5)

TABLE 2. Exercise Analysis on 'Active' versus 'Less active'

	Active (n=15)	Less Active (n=33)	p value
Warm Detection mean (SD)			
Left	34.5 (1.23)	35.7 (2.51)	p=0.06
Right	35.9 (1.59)	36.1 (1.96)	p=0.71
Cool Detection mean (SD)			
Left	30.3 (0.82)	29.8 (1.92)	p=0.24
Right	29.7 (0.90)	29.1 (3.20)	p=0.44
Hot Pain Thresholds mean (SD)			
Left	41.8 (3.08)	44.1 (3.47)	p=0.02*
Right	42.5 (2.60)	44.4 (3.20)	p=0.04*
Cold Pain Thresholds mean (SD)			
Left	14.0 (8.44)	15.2 (9.32)	p=0.59
Right	14.3 (8.47)	14.6 (9.26)	p=0.88
Vibration median (Q1-Q3)			
Left	0.08 (0.04-0.14)	0.23 (0.13-0.42)	p=0.001*
Right	0.14 (0.04-0.23)	0.24 (0.14-0.49)	p=0.001*

CHAPTER 7: DISCUSSION

This thesis includes five manuscripts that explore the potential role of physical therapy, acupuncture and exercise on chemotherapy induced peripheral neuropathy symptoms and neuropathic pain. The discussion will summarize the rationale, findings, and limitations with directions for future work.

Rationale

Chemotherapy induced peripheral neuropathy (CIPN) is a major side effect with the use of taxanes for breast cancer treatment. The etiology of this peripheral neuropathy is still unclear; however, impairment to the microtubules in the sensory nerves is the leading theory. (E. Gornstein & Schwarz, 2014; E. L. Gornstein & Schwarz, 2017; Grisold, Cavaletti, & Windebank, 2012). Treatments to date have focused mainly on pharmacological interventions for neuropathic pain with little success (Smith et al., 2013). An estimated 60% will experience lasting symptoms that affect functional activities (Brewer, Morrison, Dolan, & Fleming, 2016; Hershman et al., 2011; Park, Kim, & Hoke, 2015). As the number of patients with persistent CIPN is certain to increase, it is imperative to find ways to prevent, treat and improve their quality of life post cancer. To our knowledge, no study to date has used physical therapy to manage symptoms throughout the chemotherapy treatment process. Our first trial evaluated whether a physical therapy nerve gliding home program improved sensory nerve function and quality of life measures in participants with breast cancer. With the growing acceptance of acupuncture to manage cancer treatment side effects, our second trial aimed to answer whether electro acupuncture was effective in diminishing chronic

neuropathic pain caused by CIPN. Using Quantitative Sensory Testing, and patient questionnaires (numeric pain rating scale (NPRS) and the Disabilities of the Shoulder, Arm and Hand (DASH)), we quantified the sensory experience to evaluate the role for physical therapy and electro acupuncture in CIPN treatment. Further descriptive analysis defined the sensory phenotypes of neuropathic and non-neuropathic symptom profiles. Participants that exercised regularly versus those less active were also compared on analysis to evaluate the possible neuroprotective role of exercise.

Results

A physical therapy nerve gliding home program resulted in less reported pain (NPRS), less centralized pain (pain pressure algometry), and improved hand function (grip strength dynamometry) compared to the control group. Analysis dividing patients into neuropathic and non-neuropathic pain profiles resulted in minimal differences with respect to QST values. The neuropathic group demonstrated lower heat pain thresholds values statistically significant on the left (not right) hand. These lower values reflect age matched normative values (Gonzalez-Duarte, Lem-Carrillo, & Guerrero-Torres, 2016). Self-report data confirmed that the neuropathic group were more likely to report pain (NPRS) and impaired function (DASH). A second analysis divided participants' data into those who regularly exercised throughout treatment compared to a less active group. Participants that regularly engaged in exercise had significantly improved vibration perception, normalized heat pain thresholds bilaterally. The second trial using electro acupuncture for chronic CIPN neuropathic pain confirmed electro acupuncture was ineffective. The sham group demonstrated clinically relevant improvements in pain

consistent with the expected placebo response. Since the true treatment group did not experience at least the same response, concern was that the electro acupuncture may be maintaining pain. The trial was stopped early after discussion with the ethics chair.

Limitations and Directions for Future Research

Quantitative sensory testing is not a true objective measure as it relies on the participants' perception and subjective response (Backonja et al., 2009; Rolke et al., 2006; Walk et al., 2009). Testing can be inaccurate if the participant is distracted, and responses can be influenced by expectation and past experience. Skin biopsy has been suggested to quantify the density of intraepidermal nerve fibres (IENFD) to add to the QST data. It would be interesting to compare the IENFD of these participants to see if innervation density differences are present between the physical therapy home program, neuropathic sensory profiles and participants who regularly exercise. This, however, was not feasible for this current study, but potentially could be incorporated into future trials. Since CIPN is a small fibre neuropathy affecting the sensory fibres, QST along with self-report questionnaires are the most appropriate measures to quantify sensory perceptions. Measurement of IENFD, while objective, does not interpret the participants' sensory perceptions or accurately describe their functional limitations.

The visual analog scale (VAS) instead of the ordinal NPRS pain scale would be more sensitive as a continuous measure. It may have been specifically more helpful for data analysis avoiding the need to change the point scale to percentages.

To avoid a treatment effect the physical therapy home program was completed without follow up. We asked participants to keep a diary but only a few participants completed it. The feedback we received was that most of the treatment group completed the exercises all the way through chemotherapy but stopped once it was over. Two participants in the treatment group confirmed they did not complete any exercises with one not attending physical therapy. Both of these participants remained in analysis to reflect a real-world population. The majority of participants found the nerve gliding to be the most helpful out of all the information and education, and they reported immediate symptom relief, which we believe encouraged compliance. None the less, closer attention to the compliance and response with nerve gliding exercise is suggested for future trials.

It was unexpected that such large differences in QST measures would be uncovered on exercise sensitivity analysis. While we believed exercise had a neuroprotective role, we did not anticipate the differences would be as apparent. We would suggest activity questionnaires, quantifying metabolic equivalents, and even pedometer or accelerometry studies to be included in future trials.

Finally, our final number (n=48) was under half of the participants we were hoping to recruit. We did our best to encourage medical staff to advise patients of the trial, but for reasons unknown we were not successful. Patients with breast cancer were eager to enroll and numbers to 100 would not have been unreasonable. If we can find a way to advertise in clinics or have our trials as part of the information package to patients, this may help in the future.

These studies provide support for the use of physical therapy nerve gliding exercises to improve pain and function as well as exercise to prevent sensory neuropathy. Exercise can assist with other known taxane side effects including fatigue, mental alertness, depression, general strength, endurance, and flexibility (Baumann et al., 2013; Hayes et al., 2012; Streckmann, Kneis, et al., 2014; Streckmann, Zopf, et al., 2014). The goal of future research is to identify the specifics of exercise intensity, frequency, duration, and type to provide the most benefit for prevention and treatment of taxane induced peripheral neuropathy and neuropathic pain. We also confirmed that electro acupuncture should not be used in patients with chronic neuropathic pain from CIPN. Future research using acupuncture on other painful side effects from cancer treatment, such as joint pain from aromatase inhibitors, may provide effective relief explained by different pain mechanisms and pathways.

REFERENCES

Backonja, M. M., Walk, D., Edwards, R. R., Sehgal, N., Moeller-Bertram, T., Wasan, A., . . . Wallace, M. (2009). Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. *The Clinical journal of pain, 25*(7), 641-647. doi:10.1097/AJP.0b013e3181a68c7e; 10.1097/AJP.0b013e3181a68c7e

Baumann, F. T., Bloch, W., Weissen, A., Brockhaus, M., Beulertz, J., Zimmer, P., . . . Zopf, E. M. (2013). Physical Activity in Breast Cancer Patients during Medical Treatment and in the Aftercare - a Review. *Breast care (Basel, Switzerland), 8*(5), 330-334. doi:10.1159/000356172 [doi]

Brewer, J. R., Morrison, G., Dolan, M. E., & Fleming, G. F. (2016). Chemotherapy-induced peripheral neuropathy: Current status and progress. *Gynecologic oncology, 140*(1), 176-183. doi:10.1016/j.ygyno.2015.11.011 [doi]

Gonzalez-Duarte, A., Lem-Carrillo, M., & Guerrero-Torres, L. (2016). Normative values of quantitative sensory testing in Hispanic Latino population. *Brain Behav, 6*(7), e00466. doi:10.1002/brb3.466

Gornstein, E., & Schwarz, T. L. (2014). The paradox of paclitaxel neurotoxicity: Mechanisms and unanswered questions. *Neuropharmacology, 76 Pt A*, 175-183. doi:10.1016/j.neuropharm.2013.08.016; 10.1016/j.neuropharm.2013.08.016

Gornstein, E. L., & Schwarz, T. L. (2017). Neurotoxic mechanisms of paclitaxel are local to the distal axon and independent of transport defects. *Experimental neurology, 288*, 153-166. doi:S0014-4886(16)30400-9 [pii]

Grisold, W., Cavaletti, G., & Windebank, A. J. (2012). Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro-oncology, 14 Suppl 4*, iv45-54. doi:10.1093/neuonc/nos203; 10.1093/neuonc/nos203

Hayes, S. C., Johansson, K., Stout, N. L., Prosnitz, R., Armer, J. M., Gabram, S., & Schmitz, K. H. (2012). Upper-body morbidity after breast cancer: incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. *Cancer, 118*(8 Suppl), 2237-2249. doi:10.1002/cncr.27467; 10.1002/cncr.27467

Hershman, D. L., Weimer, L. H., Wang, A., Kranwinkel, G., Brafman, L., Fuentes, D., . . . Crew, K. D. (2011). Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. *Breast cancer research and treatment, 125*(3), 767-774. doi:10.1007/s10549-010-1278-0; 10.1007/s10549-010-1278-0

Park, J. S., Kim, S., & Hoke, A. (2015). An exercise regimen prevents development paclitaxel induced peripheral neuropathy in a mouse model. *Journal of the peripheral nervous system : JPNS, 20*(1), 7-14. doi:10.1111/jns.12109 [doi]

Rolke, R., Magerl, W., Campbell, K. A., Schalber, C., Caspari, S., Birklein, F., & Treede, R. D. (2006). Quantitative sensory testing: a comprehensive protocol for clinical trials. *European journal of pain (London, England), 10*(1), 77-88. doi:10.1016/j.ejpain.2005.02.003

Smith, E. M., Pang, H., Cirrincione, C., Fleishman, S., Paskett, E. D., Ahles, T., . . . Alliance for Clinical Trials in, O. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *Jama, 309*(13), 1359-1367. doi:10.1001/jama.2013.2813 [doi]

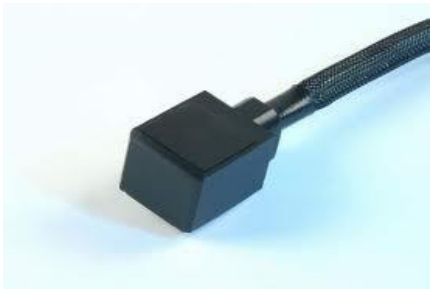
Streckmann, F., Kneis, S., Leifert, J. A., Baumann, F. T., Kleber, M., Ihorst, G., . . . Bertz, H. (2014). Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Annals of oncology : official journal of the European Society for Medical Oncology, 25*(2), 493-499. doi:10.1093/annonc/mdt568 [doi]

Streckmann, F., Zopf, E. M., Lehmann, H. C., May, K., Rizza, J., Zimmer, P., . . . Baumann, F. T. (2014). Exercise intervention studies in patients with peripheral neuropathy: a systematic review. *Sports medicine (Auckland, N.Z.), 44*(9), 1289-1304. doi:10.1007/s40279-014-0207-5 [doi]

Walk, D., Sehgal, N., Moeller-Bertram, T., Edwards, R. R., Wasan, A., Wallace, M., . . . Backonja, M. M. (2009). Quantitative sensory testing and mapping: a review of nonautomated quantitative methods for examination of the patient with neuropathic pain. *The Clinical journal of pain, 25*(7), 632-640. doi:10.1097/AJP.0b013e3181a68c64; 10.1097/AJP.0b013e3181a68c64

APPENDIX A: Thermal Quantitative Sensory Testing – TSA II Medoc

One example of thermal testing - 3 trials of warm detection, cool detection, hot pain and cold pain thresholds. This participant had cold hyperalgesia with thresholds above 18 degrees Celcius



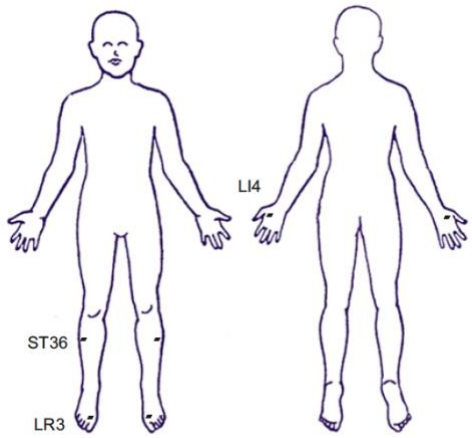
Thermode for testing index and middle finger thermal detection and thermal pain

APPENDIX B: Vibration Quantitative Sensory Testing – VSA for TSAII Medoc

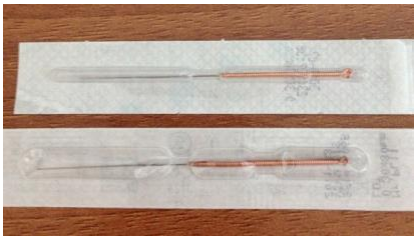
One example of vibration perception thresholds. The participant responded yes/no to sensing the stimuli

Vibration sensory analyzer for testing index finger vibration perception

APPENDIX D: Acupuncture Protocol for Chapter 4

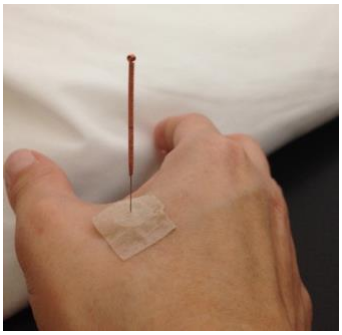


Points for acupuncture. ST36 had electro acupuncture



True acupuncture (Top) and Sham needle (below)

Protocol for all patients had needles inserted through o ring



Acupuncture for LI4 with sham needle

APPENDIX F: Assessment Forms

Pre-existing nerve entrapment as a risk factor for Chemotherapy - Induced Peripheral Neuropathy. Could there be a role for physical therapy treatment?

ASSESSMENT FORM
Patient ID#_____ Visit #_____

Surgery: Axillary Node/Sentinel Node/Lumpectomy/Mastectomy/Reconstructive surgery
Radiation Y/N Hormone therapy Y/N Immunotherapy Y/N

Chemotherapy treatment: 3 TC (no node) / 4 FECD(positive nodes)
Start date:_____

Previous upper extremity neuropathy: Y/N location_____

Chemotherapy post-cycle 2 3 4 (TC or FECD)

Changes to treatment since last visit? Y/N_____
Seeing Physical therapy or seeking treatment? Y/N _____

CIPN QUESTIONS
Any sensory changes (burning numbness/pain) in the hands? Y/N
Hand NRPS ____ /10
Has other treatment been offered to help with CIPN symptoms?_____
Any sensory changes (burning/numbness/pain) in feet? Y/N
If Yes, is it BETTER/WORSE/SAME compared to hands
DASH _____S-LANSS _____

Lymphedema: Y/N (R/L)
Volumeter: R_____ L_____

Dynamometer (dominant Hand) 1_____ 2_____ 3_____

SWMF: Index pad (R) _____(L)_____
Little pad (R) _____(L)_____

Dynamic Allodynia - Cotton pad volar/dorsal hand (R) _____ (L) _____

Algometry pressure/pain threshold Left Quadriceps _____

Nerve testing

Spurlings test (R/L Nerve Root)_____(Positive/Negative)
Phalens test (Median Nerve)_____(1 minute R/L)
Elbow Flexion Test (Ulnar Nerve)_____(2 minutes R/L)
ULTT Median Nerve (R) _____ (L)_____ (1-6)
ULTT Ulnar Nerve (R)_____(L)_____(1-6)
ULTT Radial Nerve (R)_____ (L)_____(1-6)
Tinels_____(nerve and location R or L)

QST (Left and Right Index and Middle volar DIPS)

QST	**1**	**2**	**3**	**AVG**	
Cool threshold					
Warm threshold					

QST	**1**	**2**	**3**	**AVG**
Cold Pain Threshold				
Hot Pain Threshold				

VSA (Left and Right Index volar DIP)

1	**2**	**3**	**AVG**

APPENDIX F: Assessment Forms

Electro Acupuncture in the Treatment and Management of Chemotherapy Induced Peripheral Neuropathy

ASSESSMENT FORM

Patient Study ID #_____ Cancer Stage _____

Visit: Baseline / halfway / end of trial / 2 months post HANDS or FEET

Do you believe you are in the true or sham acupuncture group?_____

Do you believe acupuncture can help your symptoms?_____

Surgical/Cancer Side_____ OR Date:_____

Surgery: Axillary Node/Sentinel Node/Lumpectomy/Mastectomy/Reconstructive surgery

Radiation Y/N Hormone therapy Y/N Immunotherapy Y/N

Chemotherapy treatment: 4 TC (no node) / 6 or 8 FECD (positive nodes) / 6 DCH

Chemotherapy Start date:_____ Chemotherapy End date:_____

Previous upper extremity neuropathy: Y/N R/L location_____

Currently receiving treatment for CIPN?_____

SSRI's?_____

U/E NRPS Baseline ____ /10 L/E NRPS Baseline ____ /10
DASH _____ LEFS_____ S-LANSS_____

Lymphedema: Y/N (R/L)

SWMF: (R) _____(L)_____ (R) _____(L)_____

Static 2-Point (R)_____(L)_____ (R)_____(L)_____

Dynamic Allodynia - (R)_____(L)_____

Algometry pressure/pain threshold Left Quadriceps _____

QST		1	2	3	AVG
Warm threshold	(R)				
	(L)				
Cool threshold	(R)				
	(L)				

QST (non-dominant)		1	2	3	AVG
Hot Pain Threshold	(R)				
	(L)				
Cold Pain Threshold	(R)				
	(L)				

VSA (index volar DIP)	Trials	AVG
Left		
Right		

APPENDIX G: Testing Instructions

QUANTITATIVE TESTS OF UPPER LIMB IN NORMAL PATIENTS TO EVALUATE THE NERVE SYSTEM RESPONSE

STUDY VARIABLES - Instructions

1) VOLUMETER

We are going to measure the volume of your hands. This gives us a measure of swelling. You need to remove watches/bracelets and any jewellery (except wedding ring) and submerge your hand very slowly into the water placing two fingers on either side of the bar. Please hold very still until the water finishes over-flowing.

2) DYNAMOMETER

This machine give us a measure of how strong your hands are. The machine does not move but records the force you are exerting. Please sit-up with elbows at your side and bent to 90^0. We will do 3 trials in each hand. When I say "go", I want you to squeeze as hard as you can (one big squeeze). Are you ready? Ready, set , go!

3) SWMF

These are small hairs that will bend with different amounts of pressure. It is a measure of the sensitivity of your fingertips to light touch. Please sit comfortably, with your eyes closed and say "touch" when you feel a filament touching you.

4) DYNAMIC ALLODYNIA

I am going to gently brush this over the back and front of your hand. Please describe the sensation (all fingers).

6) ALGOMETRY

This is a measure of tolerance to pressure. I am going to push down harder and harder on your thigh until you push the switch to stop. We want to know at what point the sensation changes for you from the feeling of pressure to a feeling of pain. We do not want to know how much pain you can tolerate. Please push the switch at the point the pressure changes to pain.

Note: Assessor in Standing and Participant sitting with legs at 90 degree angles perpendicular to the floor. Left Quadriceps measured from knee with ruler (standardardized location 7 inches from knee to mid-quads)

7) QST EVALUATION (TSAII NeuroSensory Analyzer)

WARM and COLD SENSATION

The device attached to your hand site will heat or cool. We wish to determine if you can detect these temperatures at levels appropriate for your age. The test involves either increasing or decreasing the temperature in this probe (thermode) from a neutral or baseline temperature. Keep your finger on the button so you can respond quickly. At the moment you feel either the cool/warmth, immediately press either button [NOTE TO TESTER: point to the appropriate buttons]. It is important that you press the button at the absolute first moment you detect the temperature change. Please stay alert and concentrate throughout the test. Do not press the button until you are confident that you have felt a stimulus, warm or cool change from the baseline temperature.

HEAT and COLD PAIN

The device attached to your hand site will now get hot or cold. In this test, we are interested in your perception of pain. The test involves either increasing or decreasing the

temperature in this probe (thermode) from a neutral or baseline temperature. Keep your finger on either of the two buttons so you can respond quickly. Allow the temperature to get either hotter or colder without pressing the button. Wait until the temperature becomes painful. Press either of the two buttons the instant you decide the temperature has reached a painful point. [NOTE TO TESTER: point to the appropriate buttons]. It is important that you press the button at the absolute first moment you feel pain. This is not a test of how long you can endure pain. Rather, we want to know the instant you decide the sensation is painful. Please stay alert and concentrate throughout the test.

VIBRATION

The device attached to your hand site will begin to vibrate. We wish to determine if you can detect vibration at levels appropriate for your age. The test involves either increasing or decreasing the vibration in this probe and responding yes or no if you could feel the sensation or not. There are about 14 tests in total. Please stay alert and concentrate throughout the test.