Self-Guided Online Cognitive Behavioral Strategies for Chemotherapy-Induced Peripheral Neuropathy: A Multicenter, Randomized, Wait-List Controlled Trial

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Nursing)
in the University of Michigan
2017

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DEDICATION

This dissertation is dedicated to my parents and sister for their love and support throughout my baccalaureate and doctoral education. I'd also like to dedicate this dissertation to the many friends I've made at the University of Michigan over the past seven years. Without them, I would not have had such a fantastic experience. This is Mich.

ACKNOWLEDGEMENTS

I would like to acknowledge Lynn Henry, MD, PhD for her work in developing the *PROSPECT* modules. In addition, I would like to acknowledge Mikele Garrett MBA, BBA and Celia Bridges BA, BSN, RN for their assistance in designing and editing the CIPN *PROSPECT* module, Cesar Figueras RN and Bethany LaVasseur RN, MS for their assistance in the implementation of the study procedures, and Zach Chornoby, Olivia Merrit, and Madison Vanallsburg for their assistance with data collection. I would like to acknowledge Philip Stella, MD, John C. Krauss, MD, Christine Veenstra, MD, and Grace Chen, MD for their assistance in identifying patients at the study locations.

Funding for this study was provided by the University of Michigan School of Nursing New Investigator Award. Creation of the *PROSPECT* website was supported by the Damon Runyon Cancer Research Foundation (#CI-53-10) to NLH. *PROSPECT* was adapted from the website, *Fibroguide*, which was developed with support from Grant numbers R01-AR050044 (NIAMS/ NIH), and DAMD 17-00-2-0018 (Department of Defense).

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ABSTRACT

Four in 10 individuals receiving neurotoxic chemotherapy develop chronic painful CIPN, symptoms which negatively influence physical function and may require the withdrawal of chemotherapy. However, few recommended pharmacological and no effective non-pharmacological treatments for chronic painful CIPN exist.

The purpose of this research was to examine the efficacy of a self-guided online cognitive and behaviorally-based pain management intervention called Proactive Self-Management Program for Effects of Cancer Treatment (*PROSPECT)* to reduce worst pain intensity for individuals with chronic painful CIPN. The secondary outcomes were average pain intensity, non-painful CIPN symptom severity, global impression of change, and pain interference. We also explored the mediating of effect changes in anxiety, sleep-related impairment, fatigue, and depression on improvements in worst CIPN pain intensity following *PROSPECT*.

Sixty patients with chronic painful CIPN were randomized in a 1:1 ratio to receive either eight weeks of self-guided *PROSPECT* or treatment as usual. A seven-day worst CIPN pain intensity diary and standardized measures of the secondary outcomes were administered at the baseline and eight-week time points. Mean change scores between baseline and eight-week survey data were evaluated between groups using ANCOVA adjusting for baseline. Causal mediation analyses were conducted to examine mediators of worst pain intensity improvement following *PROSPECT*.

Individuals who received the *PROSPECT* intervention had significant improvements in worst CIPN pain intensity in comparison to individuals receiving usual care (p=0.046; d=0.54) (n=38). There were no significant mean change score differences between groups for the secondary outcomes. Improvements in anxiety (β=-0.10, *CI*=-0.55–0.37) explained the greatest proportion of the treatment effect on worst CIPN pain intensity, however, none of the hypothesized mediators had a statistically significant influence on the primary outcome. (n=37).

PROSPECT improved worst pain intensity, but not secondary outcomes, in individuals with chronic painful CIPN. A larger, adequately powered study testing *PROSPECT* is needed to determine if improvements in worst pain intensity may be sustained, to evaluate *PROSPECT*'s effect on the secondary outcomes, and to identify mediators of pain-intensity-related improvement. If shown to be efficacious with further testing, *PROSPECT* may be added to pharmacological modalities for the treatment of chronic painful CIPN.

CHAPTER I

INTRODUCTION

There are approximately 14.5 million cancer survivors in the United States and many have previously received neurotoxic chemotherapy to treat oncological and hematological malignancies (American Cancer Society, 2015). Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of neurotoxic cancer treatment (e.g. platinums, vinca alkaloids, bortezomib, and taxanes) that may affect up to 68% of individuals for months to years after completion of chemotherapy (Cavaletti et al., 2013; Kautio, Haanpaa, Kautiainen, Kalso, & Saarto, 2011; Seretny et al., 2014). It is characterized by burning, numbness, tingling, and shooting sensations in the extremities (Saif & Reardon, 2005; Smith et al., 2014). In about 40% of patients, CIPN becomes chronically painful (Kautio, Haanpaa, Kautiainen, Kalso, & Saarto, 2011; Loprinzi et al., 2011; Smith, Cohen, Pett, & Beck, 2010). Chronic (lasts ≥ three months) painful CIPN results from permanent changes in the structure and functioning of the central nervous system, and is therefore defined as neuropathic pain (Baron, Binder, & Wasner, 2010; Merskey & Bogduk, 1994; Woolf, 2011). The symptoms of CIPN may negatively influence quality of life and physical functioning, and may necessitate the withdrawal of chemotherapy (Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014; Stubblefield et al., 2009).

Statement of the Problem

Despite the known negative effects that CIPN has on physical function and quality of life, there are few effective treatments for painful CIPN (Hershman et al., 2014). Due to the suboptimal effectiveness and low compliance rates associated with most pharmacological interventions for painful CIPN (Broekmans et al., 2010; Hershman et al., 2014), non-pharmacologic approaches for painful CIPN warrant further study. Use of an effective, non-pharmacologic intervention for painful CIPN may decrease the required analgesic dosage – reducing the cost and overall side effect burden for cancer survivors. One non-pharmacologic treatment used commonly for the treatment of chronic pain (e.g. back/neck, musculoskeletal, and fibromyalgia) is therapist administered cognitive behavioral pain management (Christiansen, Oettingen, Dahme, & Klinger, 2010; McBeth et al., 2012; Monticone et al., 2012; Otis et al., 2013; Thorn et al., 2011; Williams, Eccleston, & Morley, 2012). This intervention is designed to help patients self-manage pain and co-occurring symptoms such as anxiety and sleep-related impairment through cognitive and behavioral strategies such as relaxation, sleep hygiene, activity pacing, and cognitive restructuring (Ehde, Dillworth, & Turner, 2014; Kerns, Sellinger, & Goodin, 2011; Turk, Meichenbaum, & Genest, 1986). However, not all patients who may benefit can access a reputable therapist (Williams et al., 2010). One way to overcome this barrier is to offer cognitive behavioral pain management strategies in an online format. A self-guided online cognitive behavioral pain management intervention provides patients with access to symptom management resources and strategies and allows patients to practice the strategies at their own pace without the need to travel to meet with a therapist. However, a critical gap in our scientific knowledge to date is that little is known about the efficacy of self-guided online cognitive behavioral pain management interventions for painful CIPN.

Purpose

The purpose of this study was to test the efficacy of a self-guided online cognitive and behaviorally-based pain management intervention called Proactive Self-Management Program for Effects of Cancer Treatment (*PROSPECT)* to reduce worst pain intensity for individuals with chronic painful CIPN and to explore the mediating effect of *PROSPECT*-induced changes in anxiety, fatigue, depression, and sleep-related impairment on worst pain intensity. I also determined whether *PROSPECT* would improve non-painful CIPN symptom severity (e.g., numbness and tingling), pain interference, average pain severity, and patients' perceived global impression of change. Lastly, since this intervention has never been tested in individuals with painful CIPN, I assessed patients' perceptions of acceptability and satisfaction with *PROSPECT*.

Specific Aims and Hypotheses

The following describes the specific aims and hypotheses of the study. Of note, Aim 3c was added following the completion of the eight-week *PROSPECT* study to determine if baseline co-occurring symptom severity or demographic characteristics moderated improvements in worst CIPN pain intensity following *PROSPECT* usage.

Aim 1: Test the efficacy of *PROSPECT* to reduce worst CIPN pain severity in patients with chronic painful CIPN.

- Hypothesis 1: Patients with chronic painful CIPN who receive the eight-week *PROSPECT* intervention will have a greater reduction in worst CIPN pain severity than patients receiving treatment as usual (wait-list control).

Aim 2: Test the efficacy of *PROSPECT* to improve non-painful CIPN symptoms (e.g., numbness and tingling), average pain severity, pain interference, and patient global impression of change in individuals with chronic painful CIPN.

- Hypothesis 2: Patients with chronic painful CIPN who receive the eight-week *PROSPECT* intervention will have a greater improvement in CIPN symptoms, average pain severity, pain interference, and patient global impression of change scores than patients receiving treatment as usual (wait-list control).

Aim 3a: Explore the mediating effects of *PROSPECT* induced changes in anxiety, depression, fatigue, and sleep-related impairment on worst CIPN pain intensity in patients with chronic painful CIPN.

- Research Question: Will *PROSPECT*-induced changes in anxiety, depression, fatigue, and sleep-related impairment lead to reductions in worst CIPN pain intensity in patients with chronic painful CIPN?

Aim 3b: Test the efficacy of *PROSPECT* to improve anxiety, depression, fatigue, and sleep-related impairment severity in individuals with chronic painful CIPN.

- Research Question: Will patients with chronic painful CIPN who receive the eight-week *PROSPECT* intervention have greater improvements in anxiety, depression, fatigue, and sleep-related impairment than individuals receiving treatment as usual?

Aim 3c: Explore the moderating effects of low/high baseline worst pain, anxiety, depression, fatigue, and sleep-related impairment severity, gender, chemotherapy type, and low/high age on worst CIPN pain intensity improvement following eight weeks of *PROSPECT* in individuals with chronic painful CIPN.

- Research Question: Will participant baseline CIPN pain-related symptom severity or demographic characteristics moderate improvements in worst CIPN pain intensity following eight weeks of *PROSPECT*?

Aim 4: Evaluate patients' perceptions of acceptability and satisfaction related to their *PROSPECT* use.

- Research Question: Will patients with chronic painful CIPN who receive the *PROSPECT* intervention rate the intervention as helpful and easy to use?

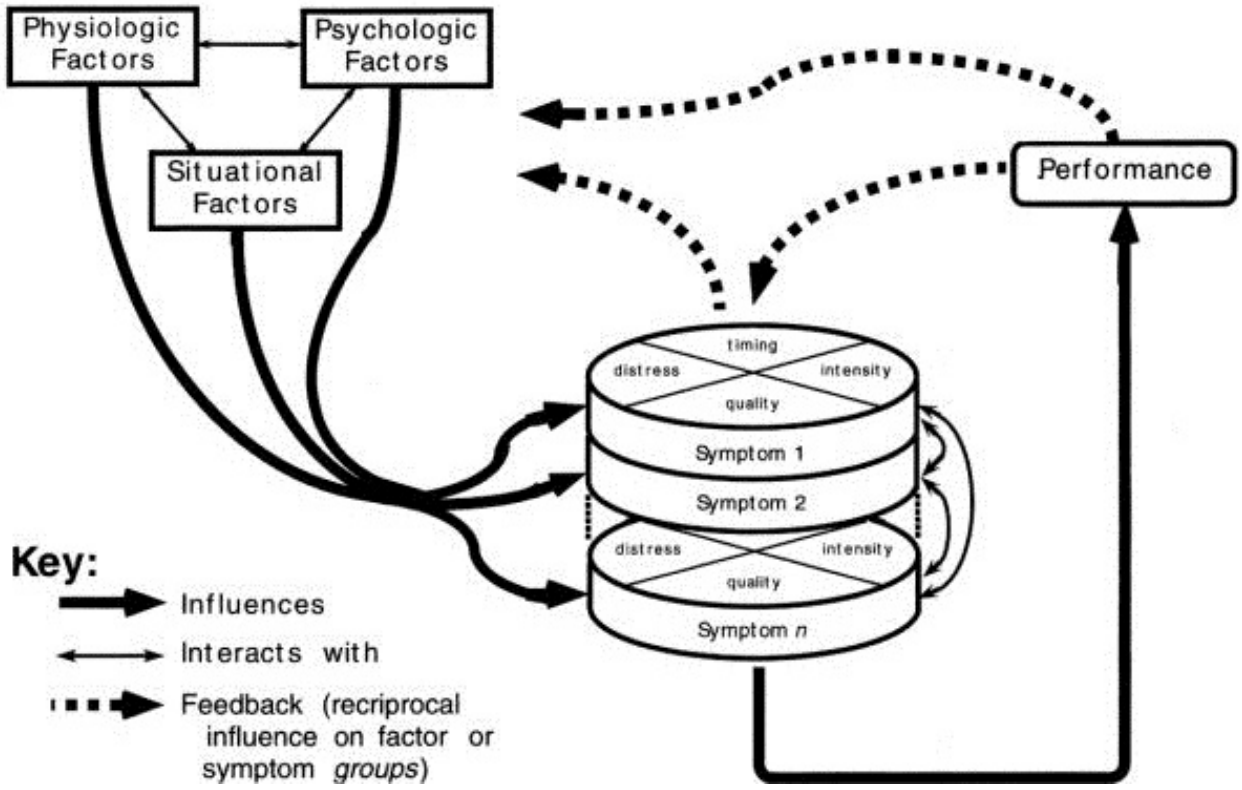
Theoretical Approach

Based on extensive research conducted with diverse chronic pain populations, several physical, psychological, and situational factors are associated with neuropathic pain severity (Alföldi, Wiklund, & Gerdle, 2014; Andersen & Kehlet, 2011; Attal, Lanteri-Minet, Laurent, Fermanian, & Bouhassira, 2011; Beck, Dudley, & Barsevick, 2005; Beijers, Mols, Dercksen, Driessen, & Vreugdenhil, 2014; Belfer et al., 2013; Bhatnagar et al., 2014; Bokhari, McMillan, McClement, & Daeninck, 2012; Borrello et al., 2006; Bruce et al., 2014; Dieleman, Kerklaan, Huygen, Bouma, & Sturkenboom, 2008; Eckhoff, Knoop, Jensen, & Ewertz, 2015; Edwards, Cahalan, Mensing, Smith, & Haythornthwaite, 2011; Ezendam et al., 2014; Glendenning et al., 2010; Hirsh et al., 2005; Honea, Brant, & Beck, 2007; Kanbayashi et al., 2010; Kroenke et al., 2013; Lewis et al., 2015; Miaskowski & Lee, 1999; Miaskowski et al., 2014; Poole, White, Blake, Murphy, & Bramwell, 2009; Reuben, Makari-Judson, & Lurie, 2004; Rustoen et al., 2004; Schou Bredal, Smeby, Ottesen, Warncke, & Schlichting, 2014; Seretny et al., 2014; Smith et al., 2015; Tofthagen, 2010; Wilson et al., 2013). The relationships among many of these influencing factors, CIPN pain severity, and functional impairment were examined in this intervention study using the Theory of Unpleasant Symptoms (TOUS) (Figure 1) (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The TOUS outlines the relationship between the physical, psychological, and situational influencing factors, symptoms, and performance outcomes to provide a framework for testing interventions to reduce the symptoms of chronic painful CIPN

(Smith & Liehr, 2008). All model components influence one another and this is illustrated in Figure 1 by the bidirectional arrows between concepts (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). Figure 2 shows how the research variables of this current study fit within the context of the TOUS.

Figure 1

The Theory of Unpleasant Symptoms

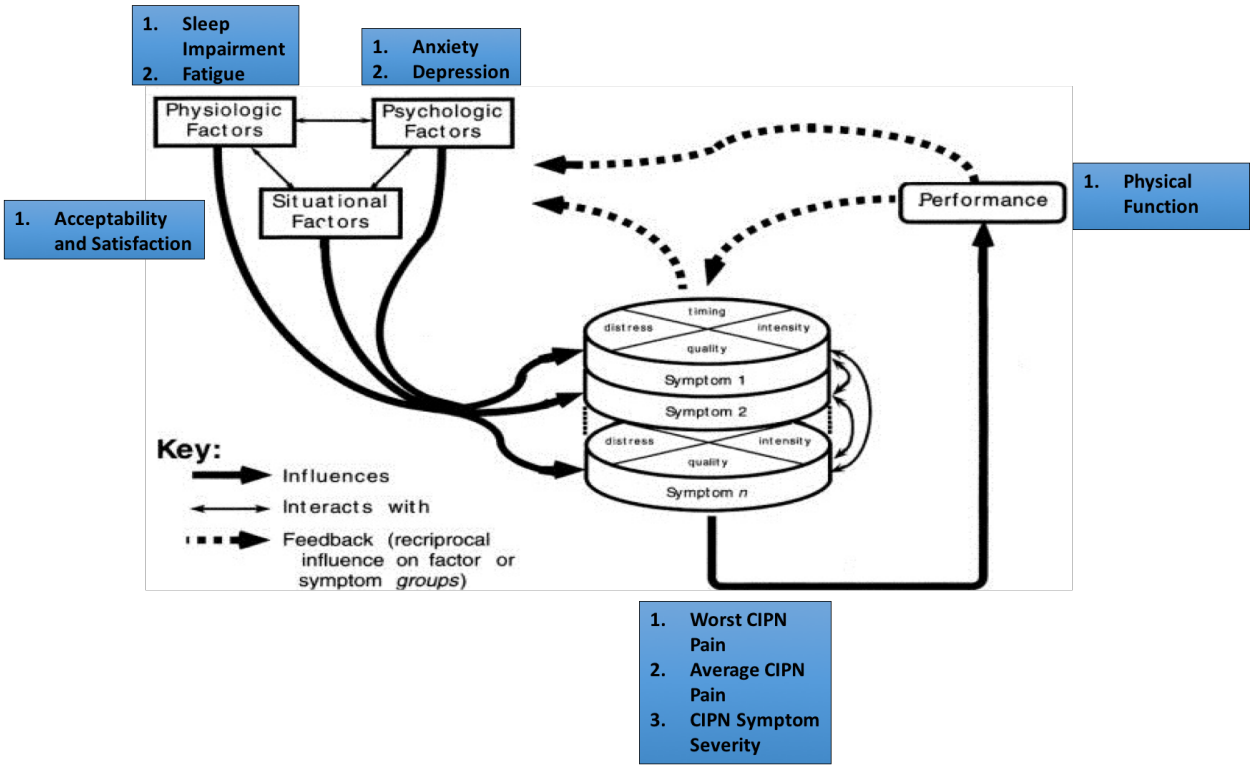


Note: The Theory of Unpleasant Symptoms model was reproduced with permission from Wolters Kluwer Health, Inc. and Copyright Clearance Center (License Number: 4096060136182) from the publication:

Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: An update. *Advances in Nursing Science, 19*(3), 14-27. Retrieved from http://ovidsp.tx.ovid.com/sp-3.24.1b/ovidweb.cgi?QS2=434f4e1a73d37e8c85021fea6c0d77318c9b254e69fa041a2ce263a0b684ef98b470ebc3cc3eb19af8b54b7ebc7a19bb01077a7b5a55fafec00fcac37f30998519b7fefa2b16f539b3eca7dceb65085c54c9c0d2ce162c6f1239ccc25fea18b7563a9a605c18a011b31e97736d0001901936c3dbd6db78ee40b1b8e72ff1a085a3cb4364668179675804572 99b3b2f17506023bc063df11b319095193847bfa9eaf2f5a74da554287983f2f51cdf9d20d72b883dfd22f50b0362b18563c9a50e1a143d3428e29777c281b6b7dd847f91d5dba3f4842a7af40e88607eba7f87f0e086bccd7f6e0ae4b59aec16eb718fc9afe065ac5c2fc7435eb0f1d8a271c5fe

Figure 2

Theoretical Model of Chronic Painful Chemotherapy-Induced Peripheral Neuropathy



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Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: An update. *Advances in Nursing Science, 19*(3), 14-27. Retrieved from http://ovidsp.tx.ovid.com/sp-3.24.1b/ovidweb.cgi?QS2=434f4e1a73d37e8c85021fea6c0d77318c9b254e69fa041a2ce263a0b684ef98b470ebc3cc3eb19af8b54b7ebc7a19bb01077a7b5a55fafec00fcac37f30998519b7fefa2b16f539b3eca7dceb65085c54c9c0d2ce162c6f1239ccc25fea18b7563a9a605c18a011b31e97736d0001901936c3dbd6db78ee40b1b8e72ff1a085a3cb4364668179675804572 99b3b2f17506023bc063df11b319095193847bfa9eaf2f5a74da554287983f2f51cdf9d20d72b883dfd22f50b0362b18563c9a50e1a143d3428e29777c281b6b7dd847f91d5dba3f4842a7af40e88607eba7f87f0e086bccd7f6e0ae4b59aec16eb718fc9afe065ac5c2fc7435eb0f1d8a271c5fe

The blue boxes describe the variables of this research that are associated with each concept of the model.

Physiological Influencing Factors

The physiological factors hypothesized to influence CIPN pain severity (Figure 2) in this study were sleep-related impairment and fatigue (Alföldi, Wiklund, & Gerdle, 2014; Andersen & Kehlet, 2011, Beck, Dudley, & Barsevick, 2005; Bhatnagar et al., 2014; Bruce et al., 2014; Eckhoff, Knoop, Jensen, & Ewertz, 2015; Ezendam et al., 2014; Glendenning et al., 2010; Honea, Brant, & Beck, 2007; Kanbayashi et al., 2010; Miaskowski & Lee, 1999; Reuben, Makari-Judson, & Lurie, 2004; Schou Bredal, Smeby, Ottesen, Warncke, & Schlichting, 2014). Sleep-related impairment co-occurs in approximately 65% of individuals with chronic pain and may also co-occur with psychological symptoms such as depression and anxiety (Alföldi, Wiklund, & Gerdle, 2014; Taylor et al., 2007; Tang et al., 2007). Sleep-related impairment also has been shown to occur in up to 24% of individuals with chronic painful CIPN (Smith et al., 2015). Fatigue is another physiological influencing factor that has been shown to be a significant predictor of chronic CIPN (Eckhoff, Knoop, Jensen, & Ewertz, 2015). Specifically, fatigue has been shown to occur in approximately 37% of individuals with chronic painful CIPN (Smith et al., 2015). Together, pain, sleep disturbance, and fatigue may occur in up to 40% of individuals with cancer (Beck, Dudley, & Barsevick, 2005; Honea, Brant, & Beck, 2007; Miaskowski & Lee, 1999). Thus, it was hypothesized that sleep-related impairment and fatigue would influence CIPN pain severity in this model.

Psychological Influencing Factors

The psychological influencing factors that are hypothesized to affect painful CIPN severity in this study are anxiety and depression. There are several studies demonstrating that anxiety and depression frequently co-occur with neuropathic pain (Attal, Lanteri-Minet, Laurent, Fermanian, & Bouhassira, 2011; Kroenke et al., 2013; Poole, White, Blake, Murphy, &

Bramwell, 2009). For example, a study conducted by Attal, Lanteri- Minet, Laurent, Fermanian, & Bouhassira (2011) demonstrated that individuals who reported neuropathic pain had more severe anxiety and depression than those who did not report neuropathic pain ($p <. 01$). Further, there have been several studies providing evidence that anxiety and depression co-occur with cancer surgery-related chronic pain (Andersen & Kehlet, 2011; Belfer et al., 2013; Bokhari, McMillan, McClement, & Daeninck, 2012; Bruce et al., 2014; Edwards, Cahalan, Mensing, Smith, & Haythornthwaite, 2011; Miaskowski et al., 2014; Schou Bredal, Smeby, Ottesen, Warncke, & Schlichting, 2014). Specifically, two studies provide evidence that anxiety and depression are significant predictors of neuropathic pain following breast cancer surgery (Andersen & Kehlet, 2011; Miaskowski et al., 2014).

Anxiety and depression have also been shown to co-occur in individuals with painful CIPN. A study by Smith et al. (2015) reported that up to 39% of individuals with chronic painful CIPN report low emotional functioning (i.e. anxiety and depression). In addition, individuals with chronic painful CIPN who have low emotional functioning were less likely to experience an analgesic effect following duloxetine treatment in comparison to patients with high emotional functioning (Smith et al., 2015). Further, a study by Beijers, Mols, Dercksen, Driessen, & Vreugdenhil (2014) found that patients who reported many CIPN symptoms on the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity Scale (FACT/GOG-Ntx) also reported significantly lower emotional well-being scores on the same scale ($p = 0.002$). Qualitative reports from patients also demonstrate that they experience a decrease in emotional functioning due to the symptoms of CIPN. In a study by Tofthagen (2010), one patient with CIPN stated, “I just get discouraged and down and … ‘cause I was always a doer, a person that was on the go doing things and I can’t … can’t do any of that” (Tofthagen,

2010). Overall, based upon the current evidence regarding the associations between anxiety, depression, and pain in individuals with cancer treatment-related chronic pain (surgery and CIPN-related), it was hypothesized that anxiety and depression would influence painful CIPN severity in this proposed study.

Situational Influencing Factors

The situational factors associated with painful CIPN in this model included acceptability and satisfaction with treatment. Acceptability and satisfaction was classified as a situational factor because it was thought that patients would continue to use the intervention if it was well accepted and they were satisfied with the content of the intervention (Hirsh et al., 2005).

Demographic, Cancer Diagnosis, and Cancer Treatment Influencing Factors

There are several demographic and cancer diagnosis and treatment factors that were hypothesized to influence chronic painful CIPN severity (Borrello et al., 2006; Dieleman, Kerklaan, Huygen, Bouma, & Sturkenboom, 2008; Lewis et al., 2015; Miaskowski et al., 2014; Rustoen et al., 2004; Seretny et al., 2014; Wilson et al., 2013). In addition, while not the focus of this section, there is evidence demonstrating that these factors also influence the physiological, psychological, and situational influencing factors of the adapted TOUS (Avis et al., 2013; Deng et al., 2016; Dhingra et al., 2015; Finney et al., 2015; Fisher et al., 2008; Kim et al., 2015; Liu et al., 2012; Stafford et al., 2016; Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003; Tantoy, Cataldo, Aouizerat, Dhruva, & Miaskowski, 2016; Thiagarajan et al., 2016; Ward et al., 2004; Westby, Berg, & Leach, 2016).

Ethnicity, comorbid chronic conditions, age, and gender are several demographic factors that may influence the severity of painful CIPN. Ethnicity and comorbid chronic conditions have been shown to influence neuropathic pain severity. For example, individuals of African

American ethnicity (*OR* = 1.78) and individuals with comorbid chronic conditions such as diabetes (*OR* = 1.98) and fibromyalgia (*OR* = 2.75) have been shown to be at a higher risk of developing neuropathic pain following breast cancer surgery (Wilson et al., 2013). Age has also been shown to influence neuropathic pain severity. A study by Miaskowski et al. (2014) demonstrated that in comparison to the "no pain" group, participants who had moderate pain following breast cancer surgery were significantly younger ($p < 0.0001$). Lastly, survey results have demonstrated that females report higher incidences and severities of neuropathic pain then men in the general population (Dieleman, Kerklaan, Huygen, Bouma, & Sturkenboom, 2008; Rustoen et al., 2004). Based on the results of these studies, it was hypothesized that ethnicity, gender, age, and comorbid medical conditions would influence painful CIPN severity.

Cancer diagnosis and treatment-related factors such as cancer and neurotoxic chemotherapy type also have been shown to influence CIPN severity. A study by Borrello et al. (2006) revealed that 15% of patients with multiple myeloma reported peripheral neuropathy prior to the administration of bortezomib. This suggests that multiple myeloma may contribute to the development of CIPN independent of neurotoxic chemotherapy receipt. Chemotherapy type has also been demonstrated to influence neurotoxicity severity. For example, individuals receiving platinum-based chemotherapy have been shown to report higher incidences of neurotoxicity in comparison to individuals who receive taxanes for the treatment of cancer ($p < 0.001$) (Lewis et al., 2015). Further, a systematic review conducted by Seretny et al. (2014) demonstrated that the type of neurotoxic chemotherapy received (i.e. bortezomib, taxanes, platinums, thalidomides, vinca alkaloids) accounted for 32% of the variance in CIPN incidence ($p < 0.04$).

Symptoms and Performance

There are several studies reporting the prevalence and negative effects of CIPN symptoms (e.g. numbness, tingling, and pain) on performance (physical function) among individuals who receive neurotoxic chemotherapy (Beijers, Mols, Dercksen, Driessen, & Vreugdenhil, 2014; Kautio, Haanpaa, Kautiainen, Kalso, & Saarto, 2011; Seretny et al., 2014). A study by Kautio, Haanpaa, Kautiainen, Kalso, & Saarto (2011) found that numbness (58%), tingling (71%), and pain (40%) of the hands and feet were the most common symptoms of CIPN. Due to the symptoms of CIPN, patients have difficulty performing daily activities such as unbuttoning clothing, picking up items from the floor, and opening jars or bottles due to weakness in the hands (Beijers, Mols, Dercksen, Driessen, & Vreugdenhil, 2014; Tofthagen, 2010). In addition, the symptoms of CIPN have been shown to be associated with decreases in quality of life (Beijers, Mols, Dercksen, Driessen, & Vreugdenhil, 2014; Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014). Based upon this evidence, the symptoms of focus for this study included worst pain severity and non-painful CIPN symptoms (e.g., numbness and tingling) and the performance outcome was physical function. Quality of life is an important aspect to measure related to pain, but quality of life is an extension of physical function because adequate function is necessary to carry out day-to-day activities and participate in social events (characteristics that may improve quality of life). Thus, quality of life was not measured separately as a component of performance.

Overall, the TOUS posits that the influencing factors and symptoms influence an individual's performance. Thus, it was hypothesized that *PROSPECT* would decrease worst CIPN pain severity due to the mediating effect of the physiological, psychological, situational (i.e. sleep-related impairment, fatigue, depression, anxiety, and acceptability and satisfaction with *PROSPECT*), demographic, and cancer diagnosis and treatment-related influencing factors.

In addition, it was hypothesized that improvements in CIPN pain intensity and non-painful CIPN symptoms (e.g., numbness and tingling) would subsequently improve overall physical function (performance outcome) (e.g. improvements in gross motor function and fine motor function).

Results

Chapter II describes a detailed summary of the incidence, pathophysiology, types, and symptoms of CIPN. In addition, a synthesis of the pharmacological and non-pharmacological interventions that have been tested to date for the treatment of CIPN is described. Chapter III is presented in manuscript form as it has been published. Due to the meager evidence surrounding efficacious non-pharmacologic treatments for the treatment of chronically painful CIPN, I conducted an integrative review to determine the effect of varying cognitive behavioral pain management doses, delivery methods, strategies, and follow-up periods on several pain and pain – related outcomes in a manuscript entitled, "Cognitive Behavioral Therapy and Chronic Pain: An Integrative Review." Chapter IV reports the results specific to Aims 1, 2, and 4. Chapter V presents the results pertinent to Aim 3. However, a summary of the study's results is presented here. Individuals receiving *PROSPECT* experienced significant reductions in worst CIPN pain intensity in comparison to individuals receiving usual care (Aim 1), but, there were no significant differences between groups for the secondary outcomes of average pain, pain interference, non-painful CIPN symptom severity (e.g., numbness/tingling), or global impression of change (Aim 2). Improvements in anxiety mediated the greatest proportion of the treatment effect of *PROSPECT* on worst CIPN pain intensity, however, none of the hypothesized mediators were significant (i.e. anxiety, depression, fatigue, sleep-related impairment) (Aim 3a). Individuals receiving *PROSPECT* did not experience significant improvements in anxiety, depression, fatigue, or sleep-related impairment in comparison to individuals receiving treatment as usual

(Aim 3b). Individuals who were older or had low baseline co-occurring symptom severity experienced the greatest improvements in worst CIPN pain intensity following *PROSPECT* usage (Aim 3c). Participants receiving *PROSPECT* also had moderate-high ratings of acceptability and satisfaction with the *PROSPECT* intervention (Aim 4). Finally, Chapter VI summarizes the results, limitations, and future directions of this research.

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CHAPTER II

TREATMENT OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY AND ASSOCIATED PAIN

Chronic Neuropathic Pain

Chronic neuropathic pain affects an estimated 100 million individuals in the United States (Institute of Medicine, 2011). Chronic neuropathic pain is defined as pain that lasts longer than three months and results from permanent changes in central nervous system processes leading to pain that persists beyond the resolution of the initial injury (Merskey, Bogduk, & International Association for the Study of Pain, 1994). Chronic pain is a problem for individuals with cancer (Smith et al., 2014), fibromyalgia (Williams et al., 2010), low back pain (Monticone et al., 2013), musculoskeletal pain (Mangels, Schwarz, Worringen, Holme, & Rief, 2009), diabetes, Parkinson's Disease, complex regional pain syndromes (Baron, Binder, & Wasner, 2010), and military veterans (Higgins et al., 2014). It is characterized by burning, shooting, and sudden pain; numbness, and paresthesias (Baron, Binder, & Wasner, 2010). Chronic pain has negative effects on quality of life (O'Connor, 2009), sleep, physical function, mood, and family and social relationships (Breivik, Collett, Vittorio, Ventafridda, Cohen & Gallacher, 2006).

Pathophysiology of Neuropathic Pain

Several mechanisms may lead to the development of neuropathic pain. Neuropathic pain usually begins with an injury of the afferent neural pathways. Following peripheral nerve injury, there is an increase in spontaneous, ongoing pain signaling in both the injured and neighboring nociceptive afferent neurons due to ectopic nerve activity. Ectopic nerve activity may occur

because of increased levels of mRNA for voltage-gated sodium channels (increases membrane excitability of nociceptive nerves) and increased expression of sodium channels among injured and neighboring intact afferent pain fibers (may lower action potential thresholds). Continuous pain signaling from peripheral afferent fibers (that release excitatory amino acids and neuropeptides within the spinal cord dorsal horn) leads to postsynaptic changes of second-order nociceptive neurons. This continual pain input eventually leads to neuronal hyperexcitability and decreased Aβ/Aδ-fiber activation thresholds within the dorsal horn in a process called central sensitization. Chronic neuropathic pain is the outcome of central sensitization and is characterized by abnormal pain sensations – allodynia and hyperalgesia – which may occur in the absence of apparent tissue injury (Baron, Binder, & Wasner, 2010; Woolf, 2011).

There are several factors that contribute to the development of central sensitization. Following the development of a nerve lesion, nerve inflammation induces the migration of macrophages into the dorsal root ganglion, which release pro-inflammatory cytokines (e.g. tumor necrosis factor) that increase pain hypersensitivity (Baron, Binder, & Wasner, 2010; Zhang et al., 2016). Activated microglia within the central nervous system also maintain neuropathic pain (increases neuronal hyperexcitability) following nerve inflammation by releasing several immune modulators (e.g. substance P and glutamate) that bind to and activate pain-projection neurons in the spinal cord dorsal horn. This release of neurotransmitters causes a long-lasting membrane depolarization in the spinal cord neurons (sensitizes nerve endings) (Latremoliere & Woolf, 2009; Richardson & Vasko, 2002; Teodoro et al., 2013). Following membrane depolarization in the spinal cord neurons, the magnesium that is normally present in the NMDA channel (of the spinal cord dorsal horn) leaves the channel and is exchanged with calcium. The introduction of calcium into the NMDA channel causes the production of nitric oxide and

prostaglandins that increase the excitability of spinal cord neurons in response to incoming nociceptive signals (Milligan & Watkins, 2009). Ultimately, these effects of NMDA activation lead to the amplification of pain messages being transmitted to higher brain areas (e.g. thalamus) (Baron, Binder, & Wasner, 2010; Milligan & Watkins, 2009). Moreover, the loss of inhibitory GABAergic interneurons in lamina II are also thought to contribute to the reduction in inhibitory control in the spinal cord dorsal horn (leads to the sensitization of peripheral afferents) (Baron, Binder, & Wasner, 2010; Lekan, Carlton, & Coggeshall, 1996; Woolf, Shortland, & Coggeshall, 1992; Woolf & Mannion, 1999; Woolf, 2011).

There are also factors related to descending pain modulation that influence the development of central sensitization. Evidence supporting descending pain modulation can be explained in the context of the Spino-Bulbo Spinal Loop (Ossipov et al., 2010, 2014; Phillips & Clauw, 2011; Suzuki, Rygh, & Dickenson, 2004; Suzuki & Dickenson, 2005). First, afferent nociceptors enter the spinal cord dorsal horn and synapse with transmission neurons. The transmission neurons ascend through the contralateral spinothalamic tract and target the thalamus and parabrachial area. Next, the nociceptive signals are transmitted to higher brain areas such as the amygdala (responsible for control of fear and mood), hypothalamus (related to sleep), and cortical areas (e.g. prefrontal cortex). Descending nociceptive transmissions from higher brain areas are then modulated through projections to the periaqueductal gray area, a source of descending opioid mediated inhibition of nociceptive inputs (Gao, Kim, & Mason, 1997; Waters & Lumb, 1997; Yeung, Yaksh, & Rudy, 1977). Next, nociceptive signals are transmitted to the rostral ventral medulla, which is thought to be the main relay site for descending influences to the spinal cord dorsal horn. The rostral ventral medulla contains “on” (increase pain) and “off” (decrease pain) cells that exert a bidirectional pain modulatory effect through the release of

descending noradrenergic and serotonergic inhibitory projections to the spinal cord (Ossipov, Dussor, & Porreca, 2010; Ossipov, Morimura, & Porreca, 2014). The role of a norepinephrine-induced nociceptive response is demonstrated by evidence suggesting that pain is decreased when norepinephrine binds with alpha 2 adrenoceptors (inhibitory action), while pain is increased when norepinephrine binds with alpha 1 adrenoceptors (Holden & Naleway, 2001; Holden, Van Poppel, & Thomas, 2002). Further, the release of 5-HT (serotonin) from the rostral ventral medulla can induce a facility or inhibitory effect on receptor cells in the spinal cord dorsal horn depending on the type of 5-HT receptor activated (e.g. activation of 5-HT3 receptors increases nociception) (Ossipov et al., 2010, 2014; Phillips & Clauw, 2011; Suzuki, Rygh, & Dickenson, 2004; Suzuki & Dickenson, 2005). It is suggested that decreases in descending pain inhibition may lead to the maintenance of chronic pain (Ossipov, Morimura, & Porreca, 2014).

Through physiological changes within the central nervous system, co-occurring physiological and psychological factors such as fatigue, sleep, depression, and anxiety also can influence the severity of neuropathic pain (Eckhoff, Knoop, Jensen, & Ewertz, 2015; Kroenke et al., 2013; Tang, Wright, & Salkovskis, 2007; Taylor, Mallory, & Lichstein, 2007). Human imaging studies reveal that there are connections between the periaqueductal gray area, amygdala, and prefrontal cortex, which provide emotional-affective modulation of pain (Hadjipavlou, Dunckley, Behrens, & Tracey, 2006; Seifert & Maihöfner, 2007; Wiech et al., 2006). For example, evidence suggests that the neurotransmitters that are involved in descending pain modulation are also involved in the development of fatigue, sleep, depression, and anxiety (e.g. serotonin and norepinephrine) (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2015; Boakye et al., 2016; Smith, Quartana, Okonkwo, & Nasir, 2009; Zhuo, 2016). Further, recent evidence has shown that individuals suffering from pain, fatigue, anxiety, depression, and sleep

problems may have reduced gray matter volume in the prefrontal cortex, a region associated with executive cognitive control (Chao, Mohlenhoff, Weiner, & Neylan, 2014; de Lange et al., 2008; May, 2011; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011). Thus, the neurotransmitter and midbrain/cortical structural changes that occur following disturbances in sleep, mood, and fatigue may lead to imbalances in descending pain modulation through the activation of "on" and "off" cells within the rostral ventral medulla (Denk, McMahon, & Tracey, 2014). The activation of "on" and "off" cells in the rostral ventral medulla may lead to a decrease in descending pain inhibition mechanisms (through the release of serotonin and norepinephrine), and subsequently, the facilitation of nociception (Denk, McMahon, & Tracey, 2014; Ossipov et al., 2010, 2014; Phillips & Clauw, 2011; Suzuki, Rygh, & Dickenson, 2004).

Finally, dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis may also play a role in the development and/or maintenance of neuropathic pain. The stress response is divided in to the sympathomedullary and HPA axis. The sympathomedullary axis releases epinephrine following sympathetic nervous stimulation of the adrenal medulla (fight or flight). The HPA axis renews the energy lost by the initial stress response by releasing cortisol to mobilize glucose reserves (Johnson & Greenwood-Van Meerveld, 2014). Initiation of the HPA stress response begins when the amygdala signals the hypothalamus to release corticotropin-releasing factor into the hypophyseal portal circulation in response to stress. Following a cascade of events, the release of corticotropin-releasing factor eventually leads to the production of cortisol, which is targeted at several sites in the body (Johnson & Greenwood-Van Meerveld, 2014). The release of corticotropin-releasing factor is halted when stress is reduced and cortisol binds to the mineralocorticoid receptor and glucocorticoid receptor in the hippocampus. However, corticotropin-releasing factor secretion is facilitated when stress persists and cortisol binds to

receptors in the amygdala (Johnson & Greenwood-Van Meerveld, 2014). Heightened stress activity in the amygdala may then influence descending pain inhibition mechanisms via direct connections with the periaqueductal gray area and rostral ventral medulla, facilitating nociception (Johnson & Greenwood-Van Meerveld, 2014). The chronic stress generated by continual pain signaling can lead to an increase in the number of axonal connections within the amygdala and fewer axonal connections within the hippocampus, thus facilitating continual HPA axis activation and cortisol production (Radley, Anderson, Hamilton, Alcock, & Romig-Martin, 2013; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002). Continual activation of the HPA axis and subsequent production of cortisol eventually leads to cortisol dysfunction (Boakye et al., 2016; Hannibal & Bishop, 2016). In the absence of functioning cortisol, peripheral nerve injury results in unchecked peripheral inflammation and increased sensitization of peripheral nociceptors (Boakye et al., 2016; Hannibal & Bishop, 2014). Lastly, chronic stress and inflammation may result in glucocorticoid-induced depletion of norepinephrine and serotonin, which leads to disruptions in inhibitory descending pain modulation (Boakye et al., 2016).

Cancer Treatment Related Neuropathic Pain

The American Cancer Society estimates that there will be approximately 1,658,370 new cases of cancer diagnosed in 2015, and many will require surgery, radiation, or chemotherapy to treat their cancer (American Cancer Society, 2015). Pain is a particularly prevalent cancer treatment-related symptom and has been reported to occur in 53 – 64% of cancer patients (van den Beuken-van Everdingen et al., 2007). Further, approximately 18.7 – 21.4% of cancer patients experience neuropathic pain due to cancer treatment. Neuropathic pain due to cancer treatment has many origins, but is mainly caused by nerve damage resulting from surgery, radiation, or chemotherapy treatment (Bennett et al., 2012). Neuropathic pain following cancer

treatment may negatively affect quality of life, sleep, function, mood, and social relationships (Breivik, Collett, Vittorio, Ventafridda, Cohen & Gallacher, 2006; O'Connor, 2009).

Chemotherapy-Induced Peripheral Neuropathy

Neurotoxic chemotherapy is used to treat a variety of cancer types and is known to cause neuropathic pain. Chronic painful CIPN is a dose-limiting toxicity that occurs in up 40% of individuals receiving neurotoxic chemotherapy agents such as platinums, vinca alkaloids, bortezomib, thalidomides, epothilones, and taxanes (Kautio, Haanpaa, Kautiainen, Kalso, & Saarto, 2011; Loprinzi et al., 2011; Smith, Cohen, Pett, & Beck, 2010). Chemotherapy-induced peripheral neuropathy negatively influences quality of life and physical functioning, and may be a dose limiting toxicity, necessitating the withdrawal or reduction of chemotherapy (Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014; Stubblefield et al., 2009). The following section describes the incidence, pathophysiology, symptoms, risk factors, and treatment of CIPN.

Incidence, Pathophysiology, Symptoms, and Risk Factors of Chemotherapy-Induced Peripheral Neuropathy

Platinum-based chemotherapy. Chronic platinum-induced peripheral neuropathy has been demonstrated to occur in up to 38% of individuals receiving platinum-based chemotherapy (Glendenning et al., 2010; Strumberg et al., 2002). Platinum-based chemotherapy (e.g. carboplatin, cisplatin, and oxaliplatin) is generally used for the treatment of colon, lung, rectal, testicular, and ovarian cancer (Argyriou, Bruna, Marmiroli, & Cavaletti, 2012). Platinum agents work to treat cancer by forming cross links with cancer DNA that prohibit DNA synthesis and repair in cancer cells (Carozzi, Canta, & Chiorazzi, 2015; Gutiérrez et al., 2010). There are two main mechanisms that have been proposed to explain the underlying pathophysiology of

platinum-induced peripheral neuropathy (Argyriou et al., 2012). First, it is proposed that the platinum compounds of the drug alter the tertiary structure of the DNA, which promotes alterations in cell-cycle kinetics that result in an upregulation of cyclin D1 expression and hyperphosphorylation of the retinoblastoma gene product. Subsequently, when differentiated postmitotic dorsal root ganglion neurons re-enter the cell cycle, apoptosis is induced (Gill & Windebank, 1998). Second, it is hypothesized that platinum-induced oxidative stress and mitochondrial dysfunction trigger neuronal apoptosis, resulting in peripheral neuropathy (Carozzi, Canta, & Chiorazzi, 2015; Zhang et al., 2007).

Platinum-induced neuropathy generally develops during treatment, but symptoms may worsen two to six months after the completion of therapy in up to 30% of patients (coasting effect) (Mangiameli et al., 2002). Early signs of platinum-induced peripheral neuropathy include decreased vibratory sensation in the toes, loss of ankle reflexes, and numbness or tingling in the fingers or toes (Argyriou et al., 2012). The incidence and severity of platinum-induced peripheral neuropathy is related to the total dose received and the dose-intensity of treatment. For cisplatin, symptoms begin after the cumulative administration of 250-350 mg/m^2, while almost all patients have objective signs of neuropathy after the cumulative administration of 500-600 mg/m^2 (single dose is approximately 50-100 mg/m^2 administered every one to four weeks for varying numbers of cycles) (Glendenning et al., 2010; National Comprehensive Cancer Network, 2016; Roelofs, Hrushesky, Rogin & Rosenberg, 1984; Thompson et al., 1984). Carboplatin-induced peripheral neuropathy occurs less frequently when using conventional doses (e.g. area under the curve 5 – 6 mg/ml/min every three weeks for six cycles when treating ovarian cancer) (Argyriou et al., 2012; National Comprehensive Cancer Network, 2016).

Oxaliplatin-induced peripheral neuropathy presents as either an acute or chronic syndrome. The cold-induced acute toxicity is characterized by paresthesia in the extremities and perioral region that appear during or hours after infusion. Additional symptoms may include cramps, throat discomfort, muscle cramps, and trouble swallowing cold items (Pachman et al., 2015). The development of chronic oxaliplatin-induced peripheral neuropathy is similar to that of usual platinum-induced neuropathy, which includes sensory loss, reduced deep tendon reflexes, and proprioception abnormalities (Argyriou, Polychronopoulos, Iconomou, Chroni, & Kalofonos, 2008; Argyriou et al., 2012; Carozzi, Canta, & Chiorazzi, 2015). The symptoms of chronic oxaliplatin-induced peripheral neuropathy resolve in about 40% of patients six to eight months after the end of chemotherapy treatment (Argyriou et al., 2008). Peripheral neuropathy is generally observed in individuals receiving a cumulative dose of 1000 mg/m^2 (a commonly used single dose of oxaliplatin is 85 mg/m^2 when treating colon cancers) (Argyriou et al., 2012; National Comprehensive Cancer Network, 2016).

Vinca alkaloid-based chemotherapy. Up to 62% of patients receiving vinca alkaloids report CIPN (Argyriou, Bruna, Marmiroli, & Cavaletti, 2012). Vinca alkaloids are commonly used for the treatment of hematological and lymphatic malignancies, as well as solid tumors (e.g. breast, ovarian, testicular, brain, and non-small cell lung tumors). This class of chemotherapy includes both natural alkaloids (e.g., vincristine and vinblastine) and semi-synthetic compounds (e.g., vindesine, vinorelbine, and vinflunine). Vinca alkaloids work to treat cancer by inhibiting microtubule dynamics in mitotic spindles, which leads to a decrease of dividing cells at the metaphase stage and subsequently, cell death. Further, vinca alkaloids prevent the polymerization from soluble dimers into microtubules, which produces the loss of axonal microtubules and alters their length, arrangement, and orientation. These changes lead to the

swelling of both myelinated and unmyelinated fibers that then alter axonal transport and result in the build-up of neurofilaments in the cell bodies and proximal axons (Argyriou et al., 2012).

Vincristine-induced peripheral neuropathy generally begins with the decrease of deep tendon reflexes followed by paresthesia. With continuing treatment, muscular weakness (ankles, fingers, and toes) and jaw pain may occur. Further, symptoms related to autonomic dysfunction such as abdominal pain and constipation may occur within a few days of drug administration (Argyriou et al., 2012; Gutiérrez et al., 2010; Verstappen et al., 2005). The severity of vincristine-induced peripheral neuropathy is related to the total amount of drug received. Patients receiving a total dose of at least 4 mg/m^2 of vincristine have some reduction or loss of ankle reflexes, while patients who have received cumulative doses of 2 – 6 mg/m^2 generally report some degree of paresthesia (standard single dose is approximately 1.4 mg/m^2 weekly for the treatment of adult non-Hodgkin's lymphoma) (Argyriou et al., 2012, National Comprehensive Cancer Network, 2015). Despite the adverse effects of vincristine-induced peripheral neuropathy, it is generally reversible when therapy is stopped. However, approximately 30% to 78% of patients may experience a coasting effect several months after the completion of treatment (Smith et al., 2015; Verstappen et al., 2005).

Bortezomib-based chemotherapy. Up to 64% of individuals receiving bortezomib develop CIPN (Argyriou, Bruna, Marmiroli, & Cavaletti, 2012). Bortezomib is a modified dipeptidyl boronic acid used as a first line treatment for individuals with multiple myeloma (standard single dose is approximately 1.3 mg/m^2 for eight cycles). This drug works to treat cancer by inhibiting the 20S proteasome complex and disrupting various cell signaling pathways (Argyriou et al., 2012). The pathophysiology of bortezomib-induced peripheral neuropathy is unclear; however, it is hypothesized that bortezomib may interfere with the transcription, nuclear

processing, transport, and cytoplasmic translation of mRNAs in dorsal root ganglion neurons (Casafont, Berciano, & Lafarga, 2010). Neural damage may also be attributed to bortezomib-induced inflammation, oxidative stress, and changes in tubulin dynamics or mitochondria function (Carozzi, Canta, & Chiorazzi, 2015).

The main symptoms of bortezomib-induced peripheral neuropathy include neuropathic pain, sensory loss in a stocking-and-glove distribution, hyporeflexia, and impaired proprioception (Gutiérrez et al., 2010). Mean neuropathic pain numerical rating scale scores in individuals with bortezomib-induced peripheral neuropathy have been reported as 7.8/10 (Cata et al., 2007). The symptoms of bortezomib-induced peripheral neuropathy usually decrease approximately three to four months post bortezomib chemotherapy completion (Richardson et al., 2009). Risk factors for the development of bortezomib-induced peripheral neuropathy include the recurrence of multiple myeloma (Badros et al., 2007), increased dose, pre-existing neuropathy, diabetes, and prior neurotoxic chemotherapy administration (e.g., vincristine) (Lanzani et al., 2008; Mateos et al., 2006; Mohty et al., 2010; Richardson et al., 2006; Velasco et al., 2010). Moreover, multiple myeloma itself can cause neuropathy from the infiltration of the nervous system by plasma cells (Denier et al., 2006; Dispenzieri & Kyle, 2005).

Taxane-based chemotherapy. Taxane-induced peripheral neuropathy has been demonstrated to occur in up to 66% of individuals receiving treatment with taxanes (Argyriou, Bruna, Marmiroli, & Cavaletti, 2012; Gutiérrez et al., 2010). Taxanes (e.g., paclitaxel and docetaxel) are generally used for the treatment of solid tumors (e.g., breast, ovarian, lung, bladder, and prostate cancer). Taxanes work to treat cancer by disrupting the microtubules of the miotic spindle and by interfering with axonal transport. These mechanisms of action lead to 1) the injury of neuronal and non-neuronal cells within the peripheral nervous system, 2)

macrophage activation in the dorsal root ganglion and peripheral nerves, and 3) microglial activation within the spinal cord (Argyriou et al., 2012), resulting in the development of peripheral neuropathy. Clinical symptoms of taxane-induced peripheral neuropathy include paresthesia, numbness, and pain in a stocking-and-glove distribution. Other objective signs of taxane-induced peripheral neuropathy include decreased vibration sensation, loss of pain and temperature sensation, and deep tendon reflex impairment (Argyriou et al., 2012). The incidence and severity of taxane-induced peripheral neuropathy is generally related to the total dose received. Severe neuropathy generally results in individuals receiving cumulative doses of 1000 mg/m^2 of paclitaxel (normal single dose is 175 mg/m^2 cycled every 21 days to treat breast cancer) or 400 mg/m^2 of docetaxel (recommended single dose is 75-100 mg/m^2 cycled every 21 days to treat breast cancer) (Lee & Swain, 2006; National Comprehensive Cancer Network, 2015). Symptoms of taxane-induced peripheral neuropathy may decrease three to four months after the completion of chemotherapy; however, severe symptoms can persist for years after treatment (Argyriou et al., 2012; Pachman et al., 2015).

Thalidomide-based chemotherapy. Thalidomide is an agent used for the treatment of multiple myeloma, renal cell carcinoma, and lymphoma, among others (Argyriou, Bruna, Marmiroli, & Cavaletti, 2012). The dose of thalidomide ranges from 200 mg to 800 mg orally (Glasmacher et al., 2006). Thalidomide's mechanism of action related to cancer treatment is unclear, however, it may work to treat cancer through angiogenesis inhibition, immunomodulation, and cytokine modulation. Similarly, it is unknown how thalidomide chemotherapy causes peripheral neuropathy (Argyriou et al., 2012). Common symptoms of thalidomide-induced peripheral neuropathy include paresthesia of the extremities, mild weakness, and reduced deep tendon reflexes (Argyriou et al., 2012; Cundari & Cavaletti, 2009).

Risk factors for the development of thalidomide-induced neuropathy may include increased cumulative dose and daily dosing (Bastuji-Garin et al., 2002; Cavaletti et al., 2004). Further research is needed to identify the long-term outcomes of thalidomide-induced neuropathy.

Epothilone-based chemotherapy. A final class of chemotherapy that causes CIPN are epothilones (e.g., ixabepilone, sagopilone, and patupilone). Epothilones such as ixabepilone are often used in the treatment of breast cancer (standard single dose is 40 mg/m^2 administered every three weeks (Trivedi, Budihardjo, Loureiro, Reid, & Ma, 2008). Up to 71% of individuals receiving epothilones have been reported to develop peripheral neuropathy (Argyriou, Bruna, Marmiroli, & Cavaletti, 2012). Like taxanes, epothilones prevent cancer cells from dividing by interfering with microtubules and inhibiting their dynamic function at the mitotic spindle (Alberti, 2013). Epothilones also may share an overlapping binding site on tubulin with taxanes (Altmann et al., 2000; Bollag et al., 1995). Thus, epothilone-induced peripheral neuropathy may also have a similar pathophysiology as taxane-induced peripheral neuropathy (Argyriou, Bruna, Marmiroli, & Cavaletti, 2012). However, further research is needed describing the clinical features, risk factors, and long term outcomes of epothilone-induced peripheral neuropathy.

Treatment of Chemotherapy-Induced Peripheral Neuropathy

Due to the complexity and subjective nature of chronic pain, the guidelines and/or position statements of several major professional organizations involved in pain research, education, and treatment endorse a multi-modal management approach that combines both pharmacological and non-pharmacological treatments for chronic pain (American Academy of Pain Medicine, 2013; American Society of Anesthesiologists Task Force on Chronic Pain Management, & American Society of Regional Anesthesia and Pain Medicine, 2010; Chou et al., 2009). However, due to the low number of studies investigating the efficacy of pharmacological

and non-pharmacological treatments for the management of chronic painful CIPN to date, national treatment guidelines for this specific chronic pain condition are few. Without strong treatment recommendations for chronic painful CIPN and the accompanying painful numbness and tingling, patients will continue to suffer decreases in quality of life and physical function (Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014; Stubblefield et al., 2009).

The authors of a systematic review recently conducted by the American Society of Clinical Oncology have summarized the state of the science surrounding the pharmacological treatment of CIPN. The review analyzed 48 randomized controlled trials testing pharmacological interventions for the prevention and treatment of chemotherapy-induced peripheral neuropathy (CIPN) in adult cancer survivors (Hershman et al., 2014), but did not examine randomized controlled trials assessing the efficacy of non-pharmacological modalities for the treatment of CIPN because so few have been conducted to date. From their review of articles found in the Medline, Embase, and Allied and Complimentary Medicine databases that had been published from database inception to the end of 2013, the authors concluded that only duloxetine 60 mg/day can currently be recommended for the treatment of chronic painful CIPN. Given that many pharmacological agents found to be ineffective for painful CIPN (e.g. nortriptyline, gabapentin, and a topical gel containing baclofen, amitriptyline HCL, and ketamine) are effective for other neuropathic pain conditions, these drugs were recommended as second-tier treatments.

To determine the efficacy of both pharmacological and non-pharmacological modalities for the treatment of CIPN, I conducted a literature review to assess the efficacy of interventions for pain and pain-related outcomes (e.g., anxiety, depression, sleep-related impairment, fatigue, quality of life, function) in randomized controlled trials conducted within the last ten years in individuals with CIPN. The population studied, intervention dose, outcomes, results, limitations,

and risk of bias of trials that tested interventions for the treatment of CIPN are summarized in Tables 14 and 15 (Appendix A-1 and Appendix A-2, respectively). Risk of bias was defined as the examination of study design features that may lead to systematic errors in results/inferences (e.g., underestimation or overestimation of an intervention's effect on the outcome) (Higgins & Greene, 2011). The risk of bias was evaluated for each reviewed trial based on criteria set forth by Hershman et al. (2014) 1) adequate randomization, 2) concealed allocation, 3) sufficient sample size, 4) similar baseline characteristics, 5) investigators/participants blinding, 6) reliable and valid measures, 7) participant retention, 8) intent-to-treat approach, and 9) insufficient conflict of interest. Studies rated as possessing a low risk of bias had no major design features (e.g., lack of randomization or underpowered sample) that may bias the results of the study or limitations that were thought to decrease the validity of the inferences. Studies rated as possessing an intermediate risk of bias were studies that experienced some design flaws, but, no single flaw was believed to definitively bias the findings. Finally, studies rated as possessing a high risk of bias had serious design flaws (e.g., high amounts of missing data or underpowered sample) that most likely biased the results of the study (Hershman et al., 2014).

Pharmacological treatment of CIPN. Eight randomized controlled trials tested pharmacological interventions for the treatment of CIPN. Many the trials were tested in individuals who had received varying types of chemotherapy. Of the eight trials, duloxetine 40 - 60 mg/day and a ketamine based gel, were shown to significantly improve CIPN in three trials.

Two separate randomized controlled crossover trials demonstrated that duloxetine is effective in improving CIPN symptoms. The Smith et al. (2013) study randomized 231 patients with chronic painful CIPN to receive either 30 mg of duloxetine for seven days followed by 60 mg of duloxetine for four weeks or placebo. Average pain was evaluated via the Brief Pain

Inventory-Short Form "average pain" item at the end of the five-week treatment period. Results revealed that individuals receiving duloxetine had significantly lower ratings of average pain compared to placebo ($p = 0.003$). However, a limitation of this trial was that there was no follow up period beyond the termination of the intervention to determine if duloxetine had sustained effects on decreasing pain intensity. In addition, there was a higher drop-out rate in individuals receiving duloxetine than in individuals receiving placebo (11% vs. 1%). There may have been a greater drop-out rate in individuals receiving duloxetine because they experienced a greater number of grade III adverse events than individuals receiving placebo. It is possible that the individuals receiving duloxetine may have known their study group assignment and dropped out of the study because they did not experience any improvements in pain from the drug. This study was rated as possessing a low risk of bias because it met several of the risk of bias benchmarks.

A second study by Hirayama et al. (2015) randomized 34 individuals who were currently receiving or had completed chemotherapy (i.e., paclitaxel, oxaliplatin, vincristine, or bortezomib) to receive duloxetine 40 mg/day or vitamin B12 1.5 mg/day for four weeks. Severity of numbness and pain was measured using a 0 – 10 visual analogue scale at the end of the four-week study period. Study results demonstrated that individuals receiving duloxetine had significant improvements in numbness ($p = 0.03$) and pain ($p = 0.04$) in comparison to the control group at the end of the study. Limitations of this study included 1) small sample size (underpowered), 2) authors did not explain the eligibility requirements related to baseline CIPN symptom severity, and 3) some participants were still receiving chemotherapy (CIPN symptoms may have progressed as neurotoxic chemotherapy cumulative dose increased). Due to these limitations, this study was rated as possessing a high rate of bias. Overall, two different doses of

duloxetine (40 mg/day and 60 mg/day) were shown to improve CIPN symptom severity in individuals who were receiving or had received varying neurotoxic chemotherapy regimens.

The efficacy of Ketamine based gel for the treatment of painful CIPN has demonstrated mixed results. Barton et al. (2011) randomized 208 individuals with chronic painful CIPN to receive either a pluronic lecithin organogel consisting of 10 mg baclofen, 40 mg amitriptyline HCL, and ketamine 20 mg or placebo that was applied twice a day to areas of painful numbness, tingling, or burning for four weeks. Results revealed that participants receiving the gel cream had significantly lower scores on the motor (p = 0.021) and sensory subscales (p = 0.053) of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN20 than individuals receiving placebo. However, there were no differences in pain intensity ratings between the two groups as measured by the Brief Pain Inventory. Limitations of this study included a high dropout rate in both study groups (approximately 25%). Also, several factors related to the delivery of the study treatment (e.g. less than optimal dose was used, patients had difficulty getting the gel to absorb into their skin, and patients' feet may have been under dosed because they were applying the treatment with their hands) may have affected treatment response. Despite the problems with treatment delivery during the trial and high participant drop out, this treatment still demonstrated positive effects on CIPN symptom severity and met several of the other criteria for determining risk of bias. Thus, this trial was rated as possessing a low risk of bias.

A study by Gewandter et al. (2014) randomized 462 individuals with acute CIPN to receive 4g of 2% Ketamine/4% amitriptyline cream or placebo for six weeks. Results demonstrated that there were no differences in average pain, numbness, or tingling severity between groups at the end of the study. A limitation of this trial was that study participants only had to have a pain duration of one month to be included in the trial. Including participants in a trial with a less than

three-month pain duration is problematic because the participants' pain may spontaneously resolve after the conclusion of chemotherapy. Pain trials should include participants who have established pain for at least three months (definition of chronic pain) to increase assay sensitivity (Dworkin et al., 2012). Despite this limitation, the study was rated as possessing a low risk of bias because it met many the other risk of bias benchmarks.

Several other drugs (i.e. amitriptyline, gabapentin, lamigotrine, cannabinoids) have been shown to be ineffective for the treatment of CIPN. Kautio, Haanpää, Saarto, & Kalso (2008) conducted a double-blind, randomized, placebo-controlled trial to investigate the use of eight weeks of low-dose amitriptyline (10 mg/day to start, maximum dose 50 mg/day) on CIPN symptoms (reported pain, numbness, and tingling via diary) in individuals with acute CIPN during neurotoxic chemotherapy treatment. Results demonstrated that low-dose amitriptyline was no more effective than placebo in reducing symptoms of painful CIPN. This trial was rated as possessing an intermediate risk of bias because the study was underpowered to detect differences in the primary outcome and some of the enrolled patients had CIPN for less than three months.

A double-blind, placebo-controlled, crossover, randomized trial authored by Rao et al. (2007) investigated the use of 2700 mg/day gabapentin vs. placebo in individuals with acute CIPN one month following the completion of neurotoxic chemotherapy treatment. Results showed no significant differences in CIPN symptom or pain severity between the two groups, as measured by the Eastern Cooperative Oncology Group Scale and average daily pain numerical rating scale. This study was rated as possessing an intermediate risk of bias because the study was underpowered to detect differences in the primary outcomes and the sample included individuals who were receiving chemotherapy and who had already completed chemotherapy. Since CIPN severity may increase during chemotherapy treatments and beyond (due to the

coasting effect), inclusion of patients who were continuing to receive chemotherapy treatment may have compromised the study's internal validity.

In another randomized, double-blind, placebo-controlled trial conducted by Rao et al. (2008), the authors randomized 131 individuals who had CIPN symptoms for at least one month duration following chemotherapy receipt to receive 300 mg/day of lamotrigine or placebo for ten weeks. Results demonstrated no significant differences in pain severity between the two groups as measured by the Brief Pain Inventory – Short Form. Limitations of this trial included that the lamotrigine group had a higher dropout rate (33%) than the placebo group (18%). Thus, participants who were experiencing no benefit from the pill they were taking may have dropped out of the study, leaving only individuals who were benefiting from the pill they were taking. In addition, the study was underpowered to detect differences in the primary outcomes and the sample included individuals who were receiving chemotherapy and had already completed chemotherapy (heterogeneity of the sample may have compromised the internal validity of the study). Due to these limitations, this study was rated as possessing an intermediate risk of bias.

Lastly, the authors of a double-blind, placebo-controlled, crossover pilot trial randomized 16 individuals to receive up to 12 daily sprays of a cannabis-based oral mucosal spray or placebo spray for four weeks (Lynch, Cesar-Rittenberg, & Hohmann, 2014). The primary outcome of the trial was pain intensity, measured on a 0 – 10 numerical rating scale. Secondary outcomes included quality of life and quantitative sensory testing. Results demonstrated that there were no significant differences between groups on any outcome at the end of the four-week period. One limitation of this study was that the participants received varying doses of the spray (self-selected dose), so it is difficult to determine if a certain number of sprays is necessary to observe an improvement in pain. This study was underpowered and thus was rated as possessing an intermediate risk of bias.

Non-pharmacological treatments for CIPN. Far fewer trials have been conducted investigating the efficacy of non-pharmacological interventions for the treatment of CIPN. Three therapies that have been recently investigated for the treatment of CIPN are acupuncture, exercise, and interferential therapy.

One systematic review and one randomized controlled trial have been recently conducted that examine the efficacy of acupuncture for the treatment of CIPN. Franconi et al. (2013) conducted a systematic review to examine the available literature surrounding the efficacy of acupuncture for CIPN. The MEDLINE, Google Scholar, Cochrane, CINAHL, and ISI Proceedings data bases were searched from database inception to 2012. The keywords searched were (acupoint* OR acupuncture OR electro-acupuncture OR electroacupuncture OR moxibustion) AND "peripheral neuropathy." From 3989 retrieved articles, only eight papers were included in the final analysis. The authors of this study reviewed one experimental animal study, four randomized controlled studies, and three case reports. Only one randomized controlled study demonstrated support for the use of acupuncture as a treatment for CIPN (Tian et al., 2011). Limitations of the reviewed studies included small sample sizes, lack of control groups, and lack of randomization.

The authors of a randomized placebo-controlled trial randomized 60 individuals who had completed neurotoxic chemotherapy (i.e., platinums, taxanes, or vinca alkaloids) and were experiencing CIPN symptoms to one of four groups 1) eight sessions of electroacupunture, 2) eight sessions of hydroelectric baths, 3 capsules a day of 100 mg thiamine/100 mg pyridoxine hydrochloride vitamin B1/B6, or 4) placebo (Rostock et al., 2013). All interventions took place over three weeks. CIPN symptom severity and extension was assessed through detailed interviews and a 0 – 10 numerical rating scale of neuropathic symptoms. Results demonstrated

that there were no significant differences between groups at the end of treatment or 84 days post randomization. This study was rated as possessing a high risk of bias because it was underpowered, reported a high placebo response, and did not explain the eligibility requirements related to CIPN severity at baseline.

The efficacy of exercise as a treatment for CIPN has been examined in one recently conducted systematic review and two randomized controlled trials. The systematic review conducted by Streckmann et al. (2014) reviewed 18 clinical trials (ten randomized controlled trials and eight controlled trials) that examined exercise interventions for the treatment of peripheral neuropathy of any kind. The authors searched the PubMed, Cochrane, and MedLine databases from April 2013 to December 2013 using key words such as, "peripheral neuropathy" and "exercise." Results revealed that nine of the studies demonstrated beneficial effects for peripheral neuropathy (i.e. gait control, balance control, and motor/sensory symptoms). Limitations of the reviewed studies included a lack of randomized controlled trials and differences in participant populations by study (not all CIPN).

There were two randomized controlled trials found in the literature that investigated the efficacy of a non-pharmacological intervention for the treatment of CIPN (Henke et al., 2014; Streckmann et al., 2014) (Table 14; Appendix A-1). The purpose of the randomized controlled trial conducted by Streckmann et al. (2014) was to investigate the efficacy of a 36-week sensorimotor, endurance, and strength training exercise program in improving CIPN in 61 individuals diagnosed with lymphoma undergoing chemotherapy treatment. Quality of life, peripheral deep tissue sensitivity, aerobic performance level, and balance control were all measured as outcome variables in this trial. Results revealed that individuals participating in the exercise intervention had significant improvements in quality of life after 12 weeks ($p = 0.03$),

but not after the completion of the entire 36-week intervention when compared to individuals receiving treatment as usual. Individuals receiving the exercise intervention also had significant improvements in balance control ($p = 0.03$), aerobic performance level ($p = 0.05$), and peripheral deep sensitivity ($p < 0.001$) when compared to individuals in the control group. This study was rated as possessing an intermediate risk of bias because the sample was underpowered and not all of the participants were receiving neurotoxic chemotherapy.

Similarly, a randomized controlled trial conducted by Henke et al. (2014) randomized 46 individuals with lung cancer that were receiving platinum-based palliative chemotherapy to receive conventional physiotherapy plus endurance and strength training or conventional physiotherapy alone (breathing exercises and manual therapy) over three cycles of chemotherapy. Difficulty with activities of daily living was assessed using the Barthel Index and quality of life was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30. Results demonstrated that individuals receiving the intervention reported significant improvements in activities of daily living and quality of life (e.g., neuropathy symptoms $p = 0.05$) in comparison to the control group. This study was rated as possessing a high risk of bias because there was a high drop out rate (only 63% of participants completed the study), it was underpowered, and they did not use strong neuropathy measurements to assess CIPN. In addition, the primary purpose of this study was not to investigate the effect of exercise on CIPN symptoms. Future studies are needed that examine the efficacy of exercise interventions with CIPN symptoms targeted as the primary outcome.

Lastly, interferential therapy, an electrophysical method that is hypothesized to inhibit nociceptive signals in small-diameter fibers by increasing activity in large-diameter Aβ fibers, was examined in one randomized controlled trial (Lindblad, Bergkvist, & Johansson, 2016).

Lindblad, Bergkvist, & Johansson (2016) randomized 67 individuals with chronic CIPN symptoms to receive weekly interferential therapy and long-wave diathermy at high power or long-wave diathermy at low power alone for 12 weeks. Pain intensity was assessed at post study and 37 weeks post randomization using a 0 – 100 numerical rating scale. In addition, nerve symptoms and balance were also assessed. Results demonstrated that there were no significant differences between groups on any outcome. This study was rated as possessing a high risk of bias because the study was underpowered and not all participants experienced pain at baseline.

Effect of tested interventions on pain-related outcomes. Based on the results of an extensive literature review, there is some evidence supporting the efficacy of pharmacological and non-pharmacological interventions in improving pain-related outcomes (e.g., physical function, quality of life, anxiety, depression, fatigue) in individuals with CIPN, but, no specific intervention can be recommended at this time. The following pain-related outcomes were measured in the twelve CIPN treatment trials 1) quality of life (eight studies), physical function (four studies), and mood (i.e. anxiety and depression) (four studies) (Barton et al., 2011; Henke et al., 2014; Kautio et al., 2008; Lindblad, Bergkvist, & Johansson, 2016; Lynch, Cesar-Rittenberg, & Hohmann, 2014; Rao et al., 2007; Rao et al., 2008; Smith et al., 2013; Streckmann et al., 2014). Only four of the eight trials demonstrated positive effects on pain-related outcomes 1) Duloxetine 60 mg/day significantly improved physical function and quality of life (Smith et al., 2013), 2) a gel consisting of 40 mg amitriptyline HCL, and ketamine 20 mg improved quality of life (Barton et al., 2011), 3 & 4) two exercise interventions improved physical function and quality of life (Henke et al., 2014; Streckmann et al., 2014). It is important to test the efficacy of interventions in improving pain-related outcomes in CIPN treatment trials because neuropathic pain often co-occurs with several symptoms (e.g. anxiety, depression, fatigue, and sleep-related

impairment) that can negatively affect quality of life and physical function (Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014; Stubblefield et al., 2009). Due to the dearth of studies testing pain-related outcome in CIPN intervention trials, further research is necessary, especially for the outcomes of anxiety, depression, fatigue, and sleep-related impairment.

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CHAPTER III

CHRONIC PAIN AND COGNITIVE BEHAVIORAL THERAPY: AN INTEGRATIVE REVIEW

Abstract

Cognitive behavioral therapy (CBT) is often used to treat chronic pain; however, more information is needed about what are the most efficacious dose and delivery methods. The aims of this review were to determine (a) which CBT doses, delivery methods, strategies, and follow-up periods have been explored in recent intervention studies of individuals with chronic pain and (b) whether the outcomes described in the selected studies were consistent with recommendations by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. The CINAHL, EMBASE, PubMed, PsycInfo, and SCOPUS databases were searched for randomized controlled trials published from 2009 to 2015 testing CBT for adults with chronic pain. Thirty-five studies were included in this review. Results revealed that CBT reduced pain intensity in 43% of trials, the efficacy of online and in-person formats were comparable, and military veterans and individuals with cancer- related chronic pain were understudied.

Background

Chronic pain affects an estimated 100 million individuals in the United States (Institute of Medicine, 2011). Chronic pain (lasting ≥ 3 months) results from permanent changes in central nervous system processes and often occurs in sites that are distant from the site of the initial injury (Merskey, Bogduk, & International Association for the Study of Pain, 1994). Consequences of chronic pain include decreased quality of life (O'Connor, 2009), impaired

sleep, decreased physical function, impaired family and social relationships, depression, and job loss (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). Cognitive behavioral therapy (CBT) is one non-pharmacological intervention that has been tested extensively as a treatment for chronic pain in randomized controlled trials to date. The overall objective of this integrative review is to explore the efficacy of CBT for the treatment of adults with chronic pain based on evidence from recently published randomized controlled trials.

The Complexity of Chronic Pain

Chronic pain is an inherently complex and subjective experience influenced by biological, psychological, and social factors (Ehde, Dillworth, & Turner, 2014). Chronic pain is difficult to treat because it often occurs alongside other symptoms such as sleep disturbance, anxiety, and depression (Attal, Lanteri-Minet, Laurent, Fermanian, & Bouhassira, 2011) that may increase pain severity and lead to further reductions in quality of life and physical function (Bair, Robinson, Katon, & Kroenke, 2003; Beesdo et al., 2010; Gupta et al., 2007; McCracken & Iverson, 2002). Anxiety and sleep disturbance co-occur in up to 45% and 53% of individuals with chronic pain, respectively (Kroenke et al., 2013; Tang, Wright, & Salkovskis, 2007; Taylor et al., 2007). In addition, depression has been shown to be associated with increased pain severity in 21% to 72% of cases (McWilliams, Goodwin, & Cox, 2004; Poole, White, Blake, Murphy, & Bramwell, 2009).

Due to the several co-occurring symptoms associated with chronic pain, optimal management of chronic pain is challenging. First line treatments for chronic pain include tricyclic antidepressants and combined serotonergic and noradrenergic antidepressants, calcium channel α2-δ ligands, and topical lidocaine (Dworkin et al., 2010; Park & Moon, 2010). However, meta-analyses suggest that only about half of patients experience clinically meaningful

pain relief from pharmacological therapies (Bjordal, Klovning, Ljunggren, & Slørdal, 2007; Finnerup, Sindrup, & Jensen, 2010; L. A. Machado, Kamper, Herbert, Maher, & McAuley, 2009; G. C. Machado et al., 2015). Furthermore, many patients discontinue pharmacological therapy due to burdensome side effects, fear of addiction, or lack of efficacy (Broekmans, Dobbels, Milisen, Morlion, & Vanderschueren, 2010; McNicol, Midbari, & Eisenberg, 2013). Given the low efficacy of pharmacological therapies for chronic pain management, multidimensional approaches that include pharmacological and non-pharmacological treatment modalities are necessary to effectively manage chronic pain and the associated comorbid medical, psychological, and psychosocial conditions (American Academy of Pain Medicine, 2013; American Society of Anesthesiologists Task Force on Chronic Pain Management & American Society of Regional Anesthesia and Pain Medicine, 2010; Chou et al., 2009).

Cognitive behavioral therapy for chronic pain is a non-pharmacological treatment that is typically delivered via individual or group counseling sessions that occur over several weeks (Ehde et al., 2014). CBT for chronic pain reduces pain perception and psychological distress by improving an individual's ability to cope with their pain (Ehde et al., 2014; Kerns, Sellinger, & Goodin, 2011). Cognitive behavioral strategies for pain include, but are not limited to, cognitive restructuring, relaxation techniques, time- or quota-based activity pacing, and sleep hygiene. Cognitive restructuring involves identifying and reframing automatic negative thoughts, and their resulting behaviors in an effort to develop more adaptive coping thoughts and behaviors (Kerns et al., 2011). Relaxation training includes strategies such as deep breathing, progressive muscle relaxation, and visualization to reduce muscle tension and alter the perception of physical pain (Kerns et al., 2011). Activity pacing is a behavioral strategy used to help individuals schedule their activities based on time or quotas (rather than based on pain) to maximize their

functionality despite persistent pain (Kerns et al., 2011). In addition, sleep hygiene refers to a variety of sleep scheduling, dietary, environmental, and activity strategies to improve sleep onset, maintenance, and quality (McCurry, Logsdon, Teri, & Vitiello, 2007).

Cognitive behavioral therapy for pain is based on the Gate Control Theory of Pain (Melzack & Wall, 1965). According to the Gate Control Theory, descending modulation from areas in the brain that govern thought (frontal cortex), emotions (limbic system), and regulatory processes (i.e., hypothalamus) influence pain transmission in the dorsal horn of the spinal cord via neurotransmitters, endogenous opiates, and hormones such as cortisol. Moreover, as an update to the Gate Control Theory, Neuromatrix Theory (Melzack, 1999) suggests that multiple sensory, cognitive, visual, and emotional inputs may disrupt the homeostasis-regulation patterns of the brain's built-in matrix of neurons (the neuromatrix), producing a prolonged stress response (i.e., cortisol release). Due to this prolonged stress response, there may be an increase of muscle, bone, and neural tissue destruction that creates the conditions necessary for varying chronic pain conditions (Melzack, 1999). Preliminary evidence from functional magnetic resonance imaging trials suggest that CBT-induced structural changes in the prefrontal cortex may lead to the release of pain-inhibiting neurotransmitters which "gate" or block pain impulse transmission from the spinal cord to the brain (Jensen et al., 2012; Seminowicz et al., 2013) Thus, CBT-mediated descending inhibitory mechanisms result in decreased pain perception (Turk, Meichenbaum, & Genest, 1983).

A recent Cochrane systematic review (n = 42 articles) conducted by A. C. Williams, Eccleston, and Morley (2012) explored the efficacy of randomized controlled trials testing psychological treatments (CBT and behavioral therapy, respectively) for adults with chronic pain. The authors searched the Cochrane Central Register of Controlled Trials, MEDLINE,

EMBASE, and Psychlit databases from their inception to September 2011 using Medical Subject Heading terms such as “Pain,” “Psychotherapy,” “Cognitive therapy,” “Behavior therapy,” “Biofeedback (Psychology),” and “Mind-Body and Relaxation Techniques.” Results revealed that when compared with treatment as usual at post-treatment, CBT had a small effect on pain intensity and disability and a moderate effect on ratings of catastrophizing and mood (anxiety and depression). When compared with treatment as usual at follow- up (6-12 months post-treatment), CBT had no effect on pain intensity, a small effect on disability and mood, and a moderate effect on catastrophizing (A. C. Williams et al., 2012).

While strong evidence from the Cochrane review (A. C. Williams et al., 2012) demonstrates that CBT is effective for chronic pain compared with treatment as usual at post-treatment, more information is needed about whether CBT’s efficacy varies based on (a) the underlying pain etiology (such as cancer vs. low back pain), (b) “dose” (duration of therapy in weeks and number of hours) or delivery method, and (c) additional pain-related outcomes in individuals with chronic pain (Bernardy, Klose, Busch, Choy, & Hauser, 2013; Eccleston et al., 2014; Ehde et al., 2014; Macea, Gajos, Daglia Calil, & Fregni, 2010; A. C. Williams et al., 2012). It is important to target the most efficacious CBT delivery methods and doses to specific chronic pain populations to effectively utilize available CBT resources. Access to CBT treatment may be limited due to lack of transportation to the clinic, beliefs that only pharmacological treatments work for pain, the negative stigma associated with psychological therapy, and lack of trained providers (Ehde et al., 2014; D. A. Williams et al., 2010). Thus, targeting optimal doses and delivery formats to specific chronic pain populations may enhance the effi- cacy, acceptance, and availability of CBT for individuals with chronic pain.

The Cochrane review conducted by A. C. Williams et al. (2012) reported on key pain-

related outcome variables, such as pain intensity, physical functioning, and mood, but did not report the effect of CBT on other pain-related outcome variables recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) such as fatigue, sleep impairment, satisfaction with treatment, and participant global impression of change at post-treatment and follow-up. The IMMPACT guidelines recommend that all chronic pain clinical trials contain six core outcome domains: (a) pain, (b) physical function, (c) emotional functioning, (d) participant rating of improvement, (e) symptoms and adverse events, and (f) participant disposition (Dworkin et al., 2005). Examining the efficacy of CBT for chronic pain on a variety of pain-related outcomes is important due to the many biological, psychological, and social influencing factors that may contribute to the chronic pain experience (Ehde et al., 2014). It is also beneficial for chronic pain trials to measure IMMPACT-related variables to evaluate the efficacy of different treatments across trials more readily (Dworkin et al., 2005). Thus, due to the known variability in CBT intervention design and delivery (A. C. Williams et al., 2012), the use of the IMMPACT domains will help determine the efficacy of the varying CBT interventions in this review on a spectrum of pain-related variables.

Purpose

The purpose of this integrative review was to determine which CBT doses (duration of therapy in weeks and number of hours), delivery methods, strategies, and follow-up periods have been explored in recent intervention studies and in which chronic pain populations. We also examined and compared these CBT intervention design features based on guidelines recommended by the IMMPACT (Dworkin et al., 2005). Overall, this integrative review furthers the results of the Cochrane review authored by A. C. Williams and colleagues (2012) by examining the efficacy of CBT for chronic pain based on: (a) specific durations and hours of

treatment, (b) delivery method, and (c) a variety of IMMPACT-related outcomes. The information provided in this review will inform future research exploring new approaches for augmenting CBT's effectiveness and expanding access to diverse chronic pain populations.

Methods

Search Method

The CINAHL, EMBASE, PubMed, PsycInfo, and SCOPUS databases were searched for randomized controlled trials published between 2009 and 2015 testing CBT interventions in adults with chronic pain. The key search terms were *cognitive behavioral therapy* and *chronic pain* (Table 1). Papers published between 2009 and 2015 were selected for this review because literature published before 2009 has already been summarized in several systematic reviews (Bernardy et al., 2013; Eccleston et al., 2014; Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; Lunde, Nordhus, & Pallesen, 2009; Macea et al., 2010; A. C. Williams et al., 2012), and the focus of this review was to formulate updated conclusions surrounding the efficacy of CBT for chronic pain based on the most recent literature.

Inclusion and Exclusion Criteria

The inclusion criteria for the selection of the articles were (a) participants were above 18 years of age, (b) randomized controlled trial, (c) English language, (d) access to the full article, (e) published between 2009 and 2015, (f) contained outcome variable of pain intensity, (g) tested CBT interventions in individuals with chronic pain (present for ≥ 3 months) and (h) compared CBT against a control condition (i.e., standard care, education only, or exercise only). Excluded articles focused on acceptance and commitment therapy or mindfulness therapy. Acceptance and commitment therapy strives to increase functioning by improving psychological flexibility (Wicksell et al., 2013). Similarly, mindfulness therapy involves the acceptance of physical pain

or psychological distress to decrease catastrophizing (Lakhan & Schofield, 2013). In contrast, CBT focuses on trying to teach individuals how to better control their thoughts and behaviors in relation to their pain (Kerns et al., 2011). Thus, acceptance and commitment therapy and mindfulness therapies were excluded in this review because when compared with CBT, these treatments decrease chronic pain severity via a slightly different mechanism.

Search Outcome

The initial search yielded 308 results. The number of studies from the CINAHL, EMBASE, PubMed, PsycInfo and SCOPUS databases were 41, 65, 63, 23, and 116, respectively (Figure 3). After removing the duplicate articles, 185 unique studies were identified (no articles were excluded due to lack of access to the full text). Next, the inclusion and exclusion criteria were applied when examining the title and abstract, reducing the number of articles to 55. Excluded studies (a) were non-randomized controlled trials; (b) tested ACT, mindfulness, or other non-CBT interventions; (c) included non-adult populations or subjects that did not have chronic pain; and (d) did not include a pain intensity measure. Seventeen more articles were excluded following a full article review, leaving 38 articles. These 38 articles were critically appraised by the primary author using the CONSORT checklist to assess for risk of bias (Schulz, Altman, & Moher, 2010). For articles that the primary author identified as containing a high risk of bias, the primary author and his advisor further discussed the articles in question and decided whether to include them in the review. After CONSORT review, three additional articles were removed due to poor study quality (Castro, Daltro, Kraychete, & Lopes, 2012; Khan, Akhter, Soomro, & Ali, 2014; Linden, Scherbe, & Cicholas, 2014). An article authored by Castro et al. (2012) was removed because the authors did not fully explain the rationale for their choice of measures, the randomization procedure, or the statistical methods. The article authored by Khan

et al. (2014) was excluded because the authors did not thoroughly describe the results of the study or the reliability and validity of the measures used. Last, an article authored by Linden et al. (2014) was removed because the authors did not elaborate on the statistical approaches used to analyze the measures, discuss the generalizability of the findings, or explicate the randomization process. After removing these three studies, 35 were retained and became the basis for this literature review.

Data Abstraction and Measurement Strategy

The following information was abstracted from the 38 studies: (a) sample size, (b) chronic pain population, (c) CBT intervention strategies, (d) control intervention design, (e) CBT dose (duration of therapy in weeks and number of hours), (f) follow-up period, (g) CBT delivery method, (h) pain intensity and other IMMPACT outcome measures, and (i) effects on IMMPACT/primary outcomes. A study was considered positive if the CBT intervention had a significant effect ($p < .05$; as reported by authors of included studies) on pain intensity in comparison with the control conditions. A study was considered positive for IMMPACT/ primary outcomes if the CBT intervention had a significant effect ($p < .05$) on at least one IMMPACT-related variable (anxiety, depression, quality of life, global impression of change, physical function, sleep disturbance, or fatigue) or other primary outcome (as specified by the authors of the included trials) in comparison with the control condition. Similarly, if a study tested two different CBT interventions, the study was considered positive if either CBT intervention had a significant effect ($p < .05$) on pain intensity or at least one IMMPACT/primary outcome in comparison with the control condition. Positive studies were then categorized based on the population studied and CBT intervention characteristics (CBT dosage, strategies, delivery method, follow-up period).

Results

Abstracted information from the 35 studies is summarized in Table 16. Furthermore, details regarding the frequency of positive studies by population, CBT intervention characteristics, and outcome variables are highlighted in Tables 2 – 5 and 16 – 17. Tables 16 and 17 are listed in Appendices A – 3 and A – 4, respectively.

Populations

The chronic pain populations of focus in the 35 studies are described in Tables 2 and 16. The sample sizes (intervention and control group combined) of the included trials ranged from 20 (Monticone et al., 2014; Otis et al., 2013; Tang, Goodchild, & Salkovskis, 2012) to 442 (McBeth et al., 2012). Mean CBT group participant ages ranged from 39.57 (Ferrando et al., 2012) to 74.59 (Nicholas et al., 2013) years. The most frequently studied population was individuals with back/neck pain, followed by the mixed etiology and fibromyalgia populations. To clarify, the mixed etiology category contained studies of participants with various chronic pain conditions (i.e., back, knee, or joint pain). There also were no studies involving individuals with cancer-related chronic pain, and only two studies focused on military veterans with chronic pain. More than half of the studies testing CBT in patients with fibromyalgia and temporomandibular disorder showed significant reductions in pain intensity. Moreover, greater than 50% of the studies that tested CBT in military veterans and individuals with back/neck pain, mixed etiology, fibromyalgia, temporomandibular (one study), and whiplash associated with chronic pain (one study) demonstrated significant effects on the IMMPACT/primary outcomes studied, respectively.

CBT Intervention Characteristics

Tables 3, 16, and 17 summarize the characteristics of the CBT interventions as described

in the selected papers. More specifically, these tables summarize the delivery methods, doses (duration of therapy in weeks and number of hours), length of the follow-up periods, and strategies tested in the CBT interventions.

Delivery methods. Table 3 outlines the frequency of studies investigating various CBT delivery methods and the effects of each method on key outcome variables. The most frequently studied delivery method was group CBT, followed by individual and online CBT, respectively. Approximately 57% or less of the trials testing in-person delivery methods reported significant effects on pain intensity; however, more than 86% of these trials reported significant effects on IMMPACT/primary outcomes. Online CBT (CBT-OL) was also studied in seven trials, and 43% and 86% of these trials found significant effects on pain intensity and IMMPACT/primary outcomes, respectively. Furthermore, three studies tested CBT delivered via telephone or self-directed CBT manual (participants were mailed the CBT treatment manual and were asked to practice the CBT strategies on their own). Zero percent of the trials testing these formats reported significant effects on pain intensity, while 50% of the trials found significant results on IMMPACT/primary outcomes.

CBT dose. Table 3 displays the number of trials testing various CBT dosages based on the total number of weeks and hours of CBT received by study participants and the doses' effects on pain intensity and IMMPACT/primary outcomes. The most frequently studied duration of CBT was six to 10 weeks (range = 2-52 weeks; Christiansen, Oettingen, Dahme, & Klinger, 2010; Monticone et al., 2013). Six to 10 weeks of CBT significantly reduced pain intensity in only 29% of the 17 trials, but had positive effects on IMMPACT/ Primary outcomes in 94% of the studies. Results revealed that higher durations of CBT (more than 20 weeks) led to significant effects on pain intensity and the IMMPACT/Primary outcomes in 75% of the four

trials testing this duration.

The most frequently studied total number of CBT hours was six to 10 total hours (range = 1-37.5 hours; Christiansen et al., 2010; Sleptsova, Woessmer, Grossman, & Langewitz, 2013). Results demonstrated that six to 10 total hours of CBT was effective decreasing pain intensity in 30% of trials; however, this dosage led to statistically significant results on IMMPACT/Primary outcomes in 90% of the 10 trials. Moreover, studies consisting of interventions testing less than six total CBT hours had positive effects on pain intensity and IMMPACT/Primary outcomes in 0% and 50% of two trials, respectively. However, interventions testing more than 20 total CBT hours demonstrated significant improvements in pain intensity and IMMPACT/ Primary outcomes in 60% and 80% of five trials, respectively.

Furthermore, nine studies were found in which the CBT dose was defined by the participant (self-directed). In these studies, CBT was administered via the Internet or a self-directed manual that allowed the participants to use the software or CBT strategies for as much as they wanted. The trials testing a self-directed format revealed significant effects on pain intensity and the IMMPACT/Primary outcomes in 25% and 88% of the trials, respectively.

Follow-up period. Twenty-eight studies tested a follow-up period beyond the termination of the CBT intervention (Table 3). Most studies followed patients for 6 months (range = no follow-up to 1 year). Trials that tested a 6-month follow-up period reported significant effects on pain intensity and the IMMPACT/Primary outcomes in 36% and 73% of 11 trials, respectively. Moreover, only six studies tested a follow-up period of 12 months. Of these six studies, 50% and 67% of the trials reported positive effects on pain intensity and IMMPACT/Primary outcomes, respectively.

CBT intervention strategies. Table 17 describes the CBT strategies used in the included

trials. The most studied CBT strategy was cognitive restructuring (91% of trials), followed by pain/psychoeducation (80% of trials), relaxation (60% of trials), and activity pacing (60% of trials), respectively. However, the strategies of the CBT interventions varied widely across studies. Additional CBT strategies used in the included studies included biofeedback, hypnosis, sleep hygiene, assertiveness training, expressive writing, relapse prevention, goal setting, graded exposure, exercise, sleep restriction, and stimulus control.

Outcome Measures and Results

Tables 4, 5, and 16 describe the measures and results of the interventions as reported by the selected papers. In particular, Table 16 describes the IMMPACT outcomes studied and the significant results of the selected studies. Table 4 summarizes the interventions' effects on IMMPACT outcomes such as pain intensity, anxiety, depression, quality of life, global impression of change, physical function, treatment satisfaction, sleep disturbance, and fatigue. In addition, Table 5 lists the most commonly used pain intensity measures in the selected studies.

Pain intensity and IMMPACT/primary outcomes studied. Table 16 lists the pain intensity and IMMPACT/Primary outcomes studied in the selected randomized controlled trials. The pain intensity measures utilized most commonly in these studies (Table 5) included 0 to 10 rating scales (34% of trials), the Multidimensional Pain Index (17% of trials), the Brief Pain Inventory (14% of trials), the McGill Pain Questionnaire (8% of trials), and the Chronic Pain Grade Questionnaire (6% of trials).

In addition to pain intensity, other primary outcomes studied included anxiety, depression, post-traumatic stress disorder symptom severity, physical function, pain intensity, pain attitudes, pain behaviors, catastrophizing, mental health, global impression of change, opioid intake, sleep disturbance, and quality of life. However, only 8 out of 35 studies

specifically targeted pain intensity as a primary outcome (Carmody et al., 2013; Chiauzzi et al., 2010; Glombiewski, Hartwich-Tersek, & Rief, 2010; Pigeon et al., 2012; Thorn et al., 2011; Vibe Fersum, O'Sullivan, Skouen, Smith, & Kvåle, 2013; Vitiello et al., 2013; D. A. Williams et al., 2010).

Intervention effects on pain intensity and IMMPACT/primary outcomes. Table 4 highlights the number of trials testing various IMMPACT outcomes and the CBT interventions' effect on the selected IMMPACT outcome variables. Pain intensity was measured in all of the trials, but only 16 of the 35 (43%) studies found significant effects. This percentage was lower than any other IMMPACT variable examined. Furthermore, CBT was shown to significantly improve IMMPACT/Primary outcome variables in 86% (30 out of 35) of the trials. Specifically, depression, anxiety, and physical function were the most frequently studied IMMPACT variables and were significantly improved by CBT interventions in 56% to 63% of the trials testing these outcomes. In addition, there were a higher number of studies reporting significant effects for the variables of sleep disturbance and global impression of change than any other outcome examined.

Discussion

This integrative review provides an overview of which CBT dose, delivery methods, follow-up periods, and strategies have been explored in recent intervention studies, and in which chronic pain populations. We also evaluated whether the CBT outcome variables described in the selected 35 studies align with those that have been recommended by the IMMPACT guidelines (Dworkin et al., 2005). Eight key findings emerged from the 35 randomized controlled trials: (a) additional studies are needed to test CBT interventions in individuals with cancer-related chronic pain and military veterans; (b) the optimal dose of CBT is unclear; (c) online cognitive

behavioral therapy (CBT-OL) effectiveness may be comparable with traditional formats of CBT such as individual or group therapy; (d) less than 50% of the included trials reported positive effects on pain intensity; (e) future studies are needed to investigate CBT's effects on anxiety, quality of life, sleep disturbance, treatment satisfaction, global impression of change, and fatigue in individuals with chronic pain; (f) additional research is needed to investigate mediators of pain intensity improvement following CBT treatment; (g) further studies are needed to examine the long-term efficacy of CBT for pain intensity in individuals with chronic pain; and (h) future research is needed to compare the efficacy of CBT treatment strategies. Additional details regarding these eight key findings are highlighted below.

The findings of this review revealed that the fibromyalgia, veteran, temporomandibular, arthritis, and cancer-related chronic pain populations were the least frequently studied. Surprisingly, results revealed that there were no trials testing CBT for individuals with cancer-related chronic pain. Due to the high incidence and debilitating consequences of cancer-related chronic pain, further research is needed to improve treatment in this population. In fact, 19% to 39.1% (Bennett et al., 2012) of individuals with cancer experience chronic pain due to the disease and its treatment (surgery, neurotoxic chemotherapy, radiation therapy; Smith et al., 2014). In addition, cancer treatment–related chronic pain commonly co-occurs with depression, anxiety, sleep disturbance, and physical impairment (Andersen & Kehlet, 2011; Belfer et al., 2013; Miaskowski et al., 2014; Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014). While this current review revealed that there are no randomized controlled trials testing CBT for individuals suffering from cancer-related chronic pain, a meta-analysis authored by Tatrow and Montgomery (2006) revealed that cognitive behavioral strategies were effective in reducing pain (d = .49) and distress (d = .31) in individuals with breast cancer (Tatrow &

Montgomery, 2006). In addition, Kwekkeboom and colleagues (2012) conducted a pilot randomized controlled trial to assess the efficacy of guided imagery and relaxation techniques in individuals with advanced cancer. This trial found positive significant results for CBT to treat the acute pain, fatigue, and sleep symptom cluster of cancer but was not included in this review because it did not specifically enroll individuals with chronic pain. Thus, there is preliminary evidence that CBT strategies are beneficial for individuals with cancer, but further research is needed to test CBT in individuals with cancer-related chronic pain.

Furthermore, due to improvements in battlefield armor, military medicine, and combat evacuation, a greater number of returning Operational Enduring Freedom and Iraqi Freedom veterans face the challenges of chronic pain (Clark, Bair, Buckenmaier, Gironda, & Walker, 2007). Nearly 50% of veterans report chronic pain (Gironda, Clark, Massengale, & Walker, 2006), and musculoskeletal pain is the most commonly reported pain complaint of returning Operational Enduring Freedom and Iraqi Freedom veterans (Higgins et al., 2014). In addition, military veterans are a unique chronic pain population due to their high incidence of comorbid post-traumatic stress disorder and traumatic brain injury (Lew et al., 2009). This triad of chronic pain, post-traumatic stress disorder, and traumatic brain injury is called post- deployment multi-symptom disorder. In fact, in a sample of Operational Enduring Freedom and Iraqi Freedom veterans (n = 340), 42.1% were diagnosed with post-deployment multi-symptom disorder (Lew et al., 2009). Despite the complexity of the chronic pain experience faced by military veterans, only two (Carmody et al., 2013; Otis et al., 2013) of the 38 studies tested a CBT intervention in military veterans. Due to the number of military veterans returning from overseas combat with chronic pain, additional randomized controlled trials are needed to explore the efficacy of CBT in this population.

Results revealed that the most commonly studied duration of treatment was six to 10 weeks, and the most frequently studied total number of CBT hours was six to 10. CBT effectiveness varied widely based on the total number of weeks and hours of CBT received by study participants. For example, when examining CBT effects at various dosages (treatment duration), the percentage of trials reporting positive effects for pain intensity range from 0% (1-5 weeks) to 75% (>20 weeks). In addition, there was only one study that compared one CBT dose with another (Mangels, Schwarz, Worringen, Holme, & Rief, 2009). This study demonstrated that a 4-week group CBT program did not result in significantly different participant ratings of depression or quality of life when compared with a 4-week group CBT program with subsequent booster sessions (seven additional CBT sessions over 12 months; Mangels et al., 2009). The lack of studies comparing CBT dosages in the current research evidence makes it difficult to recommend an optimal course of therapy. However, as randomized controlled trials show that six to 10 weeks and six to 10 total hours of CBT demonstrate positive effects on IMMPACT/Primary outcomes, perhaps a similar dosage should be defined as "standard" in future research. Defining a standardized CBT dose will allow for the comparison of CBT studies across trials.

Regarding the efficacy of online delivery methods, results of this review demonstrated that CBT-OL is effective for individuals with fibromyalgia (D. A. Williams et al., 2010), back/neck pain (Buhrman, Nilsson-Ihrfeldt, Jannert, Strom, & Andersson, 2011; Carpenter, Stoner, Mundt, & Stoelb, 2012), and mixed etiology chronic pain (Buhrman et al., 2013; Dear et al., 2013; Ruehlman, Karoly, & Enders, 2012). Specifically, randomized controlled trials suggest that CBT-OL is effective for the management of chronic pain based on the following: (a) CBT-OL significantly improves IMMPACT/ Primary outcomes compared with a control condition, (b)

CBT-OL's positive effects persist more than 6 months beyond treatment completion (Buhrman et al., 2013; D. A. Williams et al., 2010), and (c) CBT-OL users are satisfied with the online format (Carpenter et al., 2012; Dear et al., 2013; D. A. Williams et al., 2010). These findings are consistent with prior systematic reviews that have demonstrated that CBT-OL significantly improves pain and pain-related outcomes such as anxiety and disability when compared with control conditions (Eccleston et al., 2014; Macea et al., 2010).

Analysis of CBT delivery methods revealed that there was a comparable number of CBT-OL and in-person CBT intervention studies reporting positive effects on pain intensity and IMMPACT/Primary outcomes. The efficacy of CBT-OL versus in-person CBT has been recently examined in a random- ized controlled trial. While not included in this review because it compared two active CBT treatments, de Boer, Versteegen, Vermeulen, Sanderman, and Struys (2014) conducted a randomized controlled trial comparing CBT-OL with in-person group CBT in individuals with non-specific chronic pain and found that participants in the CBT-OL group had significantly greater reductions in catastrophizing, pain intensity, pain coping, and in some aspects of quality of life compared with group CBT. One limitation of this study was that more patients dropped out of CBT-OL treatment (33.3%) than group CBT treatment (6.7%). If patients dropped out due to perceived low efficacy, this may have compromised the study's internal validity. Furthermore, a systematic review by Macea and colleagues (2010) uncovered a 26.6% dropout rate in 11 randomized controlled trials testing CBT-OL for chronic pain. Despite the higher dropout rates reported in CBT-OL trials, an online delivery method is a potential solution to the accessibility barriers inherent with individual or group CBT because it can be delivered via the participant's personal computer, tablet, or smartphone. Additional research is needed to determine whether CBT-OL is equivalent or superior to in-person CBT and to determine CBT-

OL's efficacy as a treatment for various types of chronic pain.

This review revealed that CBT significantly improved pain intensity in 43% of the trials. The low number of positive trials may be related to study design limitations. First, pain intensity was only studied as the primary outcome in eight of the included trials. Thus, the CBT interventions of the included studies may have been designed to target a co-occurring psychological symptom and were not powered to detect changes in pain intensity. Second, 17 studies included in this review compared CBT with another active intervention and not with a true control group. This limitation has been previously described by A. C. Williams and colleagues (2012) in their systematic review which revealed that CBT was not effective in significantly reducing chronic pain intensity when compared with active controls (A. C. Williams et al., 2012). Third, internal validity threats such as attrition (Carpenter et al., 2012; Chiauzzi et al., 2010; Jungquist et al., 2010), invalid statistical conclusions due to small sample size, or multiple statistical analyses (Andersson, Johansson, Nordlander, & Asmundson, 2012; Dunne, Kenardy, & Sterling, 2012; Heutink et al., 2012; Jungquist et al., 2010; Liedl et al., 2011; McBeth et al., 2012; Monticone et al., 2014; Naylor, Naud, Keefe, & Helzer, 2010; Nicholas et al., 2013; Otis et al., 2013; Pigeon et al., 2012; Thorn et al., 2011; Vitiello et al., 2013; Zachariades, 2012) may have influenced the findings of these studies. For example, a negative trial authored by Chiauzzi et al. (2010) had a higher dropout rate in the CBT intervention group than in the control group, which may have decreased the statistical validity of the analyses. Future research designed to overcome limitations such as these are necessary to further assess the efficacy of CBT for pain intensity.

The IMMPACT guidelines recommend assessing pain intensity together with several other variables—physical functioning, emotional functioning, treatment satisfaction, and

participant ratings of global improvement (Dworkin et al., 2005). Pain intensity, physical function, and depression were studied in over 75% of the trials. However, anxiety, quality of life, sleep disturbance, treatment satisfaction, global impression of change, and fatigue were all studied in less than 50% of the trials. Measuring the core IMMPACT domains in chronic pain in future trials may allow for the comparison of outcomes across trials, allow the pooling of data from different trials, and lead to the identification of optimal measures for these domains (Dworkin et al., 2005). Most importantly, inclusion of multiple IMMPACT-recommend outcome measures in future studies will allow researchers to describe CBT's multifaceted benefits.

Furthermore, regarding IMMPACT variables, sleep, fatigue, depression, and anxiety improved in over 50% of the studies testing these variables. Perhaps there are specific pain-related variables that mediate improvements in pain intensity following CBT treatment in different pain populations. For example, a study conducted by McCracken, Gross, and Eccleston (2002) identified that improvements in pain intensity, pain interference, and depression were mediated by improvements in pain-related anxiety in individuals with chronic low back pain receiving CBT. As sleep, fatigue, depression, and anxiety significantly improved in a majority of the studies, perhaps these pain- related variables are ideal candidates to be targeted in future CBT interventions as mediators of pain intensity. For instance, pain intensity and anxiety both significantly improved following a 12-week group CBT intervention (Vibe Fersum et al., 2013). Similarly, pain intensity, anxiety, and fatigue all significantly improved after individuals with fibromyalgia engaged in a 10-week group CBT intervention (van Koulil et al., 2010). The identification of chronic pain mediators may help tailor specific CBT interventions and strategies for specific pain-related variables to ultimately improve pain intensity in individuals with chronic pain and increase the availability of limited CBT resources.

In terms of the lasting effects of CBT, 73% and 36% of the studies that evaluated outcomes at a 6-month follow-up period demonstrated sustained improvements in IMMPACT/Primary and pain intensity outcomes, respectively. Six studies were designed to evaluate the lasting effects of CBT at 12 months follow-up. Results demonstrated that over 67% and 50% of these studies revealed significant effects on IMMPACT/Primary outcomes and pain intensity, respectively. These findings are consistent with the Cochrane review published by A. C. Williams and colleagues (2012) which demonstrated that CBT had no significant effects on pain intensity 6 to 12 months post-treatment, but had a small and moderate effect on mood and catastrophizing 6 to 12 months post-treatment compared with treatment as usual. Overall, the results of this current review suggest that the benefits of CBT may extend at least 6 months from the start of therapy, but more studies are needed exploring whether effects can be sustained long term, and what types of maintenance programs may be required to maintain effects for improvements in pain intensity over time.

The strategies of the CBT interventions varied widely across studies. There were six studies designed to compare CBT treatment strategies (Castel, Cascón, Padrol, Sala, & Rull, 2012; Glombiewski et al., 2010; Liedl et al., 2011; McBeth et al., 2012; Pigeon et al., 2012; van Koulil et al., 2010), however, only three of these studies (Castel et al., 2012; Glombiewski et al., 2010; Liedl et al., 2011) compared CBT treatment strategies directly against one another. For example, a trial conducted by Castel et al. (2012) demonstrated that CBT (strategies included pain education, cognitive restructuring, sleep hygiene, assertiveness training, and activity pacing) plus hypnosis was superior in improving pain intensity and psychological distress compared with CBT alone in individuals with fibromyalgia. However, while not included in this review because the study did not contain a treatment as usual control group, a study conducted by Kerns et al.

(2014) compared tailored individual CBT (used motivational enhancement strategies to encourage skill learning and practice) against standard individual CBT and found no significant differences in treatment adherence, pain intensity, physical function, or depression. Additional research is needed comparing CBT treatment strategies to determine whether a certain battery of strategies is most efficacious for individuals with chronic pain. The identification of optimal CBT strategies may lead to the development of a standard CBT protocol that can be tailored to specific chronic pain etiologies.

The limitations of this integrative review include the lack of a team approach to review and critically appraise the articles included in the study. Only the primary author reviewed the studies included in this review, thus increasing the risk of bias. It is also possible that we failed to find key studies testing CBT interventions for chronic pain. However, consistent key terms and limits were used to search each of the five databases (Table 1). Last, limiting our search to papers published from 2009 to 2015 may have resulted in the exclusion of key papers that if included in this review, may have changed the scope of our findings.

In conclusion, this integrative review examined which CBT intervention characteristics and outcome variables have been explored in recent randomized controlled trials, and in which chronic pain populations. The results of this review demonstrated that CBT was effective for pain intensity in 43% of the trials and was an effective treatment for many pain-related variables recommended by IMMPACT such as physical functioning, anxiety, depression, and quality of life. Future research is needed to refine a standardized CBT dose and to test CBT interventions in understudied chronic pain populations such as military veterans and individuals with cancer treatment–related chronic pain. Furthermore, CBT-OL was shown to be particularly promising alternative to traditional CBT because the online delivery format was comparable with in-person

CBT delivery methods for improving pain and pain-related symptoms. A logical next step based on the results of this review is to test a CBT-OL intervention in individuals with cancer treatment–related chronic pain or military veterans. If effective, CBT-OL could be further tested in combination with pharmacological interventions to improve pain and quality of life.

Acknowledgement

This Chapter was generated from an article published in the Western Journal of Nursing Research (SAGE Publishing) in 2015 by the author of this dissertation document. The table and figure numbers of this article have been updated to reflect the numbering system of this dissertation. The footnote of each table and figure listed within Chapter III states the original numbering as specified by the published manuscript. I would like to acknowledge my co-authors of the published manuscript, Ellen Lavoie Smith, PhD, APRN, AOCN®, FAAN and James Weisberg, PhD, for their help in the writing of the manuscript.

The citation for the published article is as follows:

Knoerl, R., Lavoie Smith, E. M., & Weisberg, J. (2015). Chronic Pain and Cognitive Behavioral Therapy: An Integrative Review. *Western Journal of Nursing Research*, (Journal Article). http://doi.org/0193945915615869 [pii]

Table 1

Search Terms

Databases Searched	**Search Terms**
CINAHL	(cognitive behavior* therap* OR MH cognitive therapy) AND (chronic pain OR MH chronic pain) Limits: Full text, English, randomized controlled trial, adults over 18 years of age, and last five years.
EMBASE	(‘chronic pain’/exp OR ‘chronic pain’) AND ((‘cognitive therapy’/exp OR cognitive NEAR/3 therap* OR (cognitive AND behavior?r* AND (‘therapy’/de OR therapies OR therapeutic*)) Limits: 2009-2014, Embase only, adults over 18 years of age, randomized controlled trial, and English language.
PubMed	((((“cognitive therapy”[MeSH Terms]) OR (cognitive behavior* AND (therapy OR therapies OR therapeutic))))) AND (“chronic pain”[MeSH Terms] OR “chronic pain”[All Fields]) Limits: Full text, English, randomized controlled trial, adults over 18 years of age, and last five years.
PsycINFO	(cognitive behavior* therap* OR MH cognitive therapy) AND (chronic pain OR MH chronic pain) AND “randomized controlled trials” Limits: Full text, English, randomized controlled trial, adults over 18 years old, and last five years.
SCOPUS	(cognitive behavioral therap* AND chronic pain) Limits: Article, English, randomized controlled trial, adults over 18 years of age, and last five years.

Note: “MH”= Main Heading
“MeSH”= Medical Subject Heading
This table is Electronic Supplementary Table 1 from Knoerl, Smith, & Weisburg (2015).

Table 2

Populations Testing CBT Interventions

Population	Frequency (n)	Positive Effects on Pain Intensity (%)	Positive Effects on IMMPACT/Primary Outcomes (%)
Mixed Etiology Chronic Pain	11	36%	82%
Back/neck pain	13	38%	85%
Fibromyalgia	6	50%	100%
Arthritis	1	0%	100%
Veterans	2	50%	50%
Temporomandibular Disorder	1	100%	100%
Whiplash	1	0%	100%

Note: This table is Electronic Supplementary Table 2 from Knoerl, Smith, & Weisburg (2015).

Table 3

CBT Intervention Characteristics

Duration (Weeks)	**Frequency (*n*)**	**Positive Effects on Pain Intensity (*%*)**	**Positive Effects on IMMPACT/Primary Outcomes (*%*)**
One to Five	6	0%	83%
Six to Ten	17	29%	94%
Eleven to Fifteen	7	71%	86%
Sixteen to Twenty	1	0%	0%
Over Twenty	4	75%	75%
Total Number of Hours			
One to Five	2	0%	50%
Six to Ten	10	30%	90%
Eleven to Fifteen	7	43%	86%
Sixteen to Twenty	2	100%	100%
Over Twenty	5	60%	80%
Self-Directed	9	25%	88%
CBT Delivery Method			
Individual	11	36%	91%
Group	14	57%	86%
Online	7	43%	86%
Other	3	0%	50%
Length of Study Follow-Up*			
None	7	N/A	N/A
Less than 3 month	1	100%	100%
3-4 Months	6	66%	100%
Six Months	11	36%	73%
8-9 Months	4	50%	100%
Twelve Months	6	50%	67%

Note: *Time from Baseline to Final Outcome Measure
This table is Table 2 from Knoerl, Smith, & Weisburg (2015).

Table 4

IMMPACT Variables Measured

Outcome Variable	**Frequency (*n*)**	**Percentage of Total Studies (%)**	**Studies Reporting Positive Effect (%)**
Pain Intensity	35	100	43%
Anxiety	18	47%	56%
Depression	29	80%	57%
Quality of Life	15	43%	47%
Global Impression of Change*	6	13%	100%
Physical Function	30	86%	63%
Treatment Satisfaction	16	46%	100%
Sleep Disturbance	9	24%	89%
Fatigue	9	24%	55%

Note: * There were only 5 studies that evaluated changes in Global Impression of Change scores between the CBT intervention and control groups

This table is Electronic Supplementary Table 3 from Knoerl, Smith, & Weisburg (2015).

Table 5

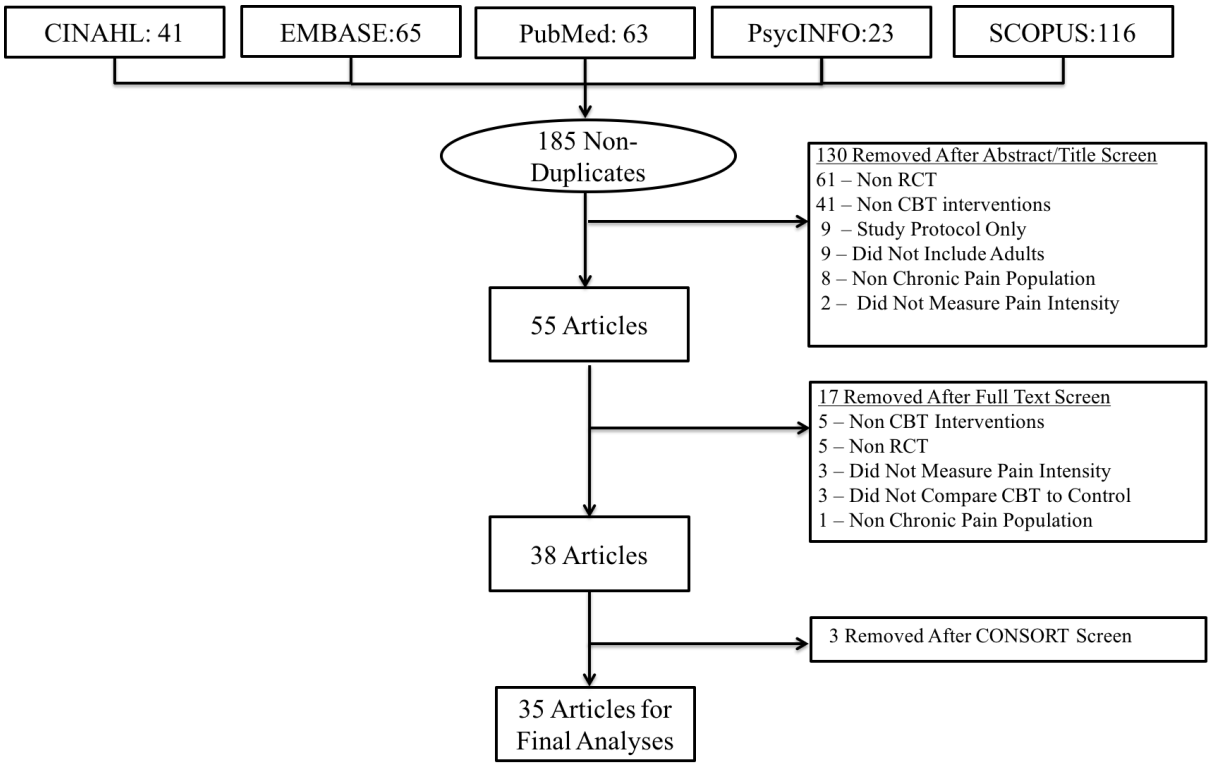
Frequency of Types of Pain Intensity Measures

Pain Intensity Measure	Frequency (*n*)	Interventions
Zero to Ten Rating Scale	13	(Carpenter et al. 2012); (Castel et al. 2012); (Christiansen et al. 2010); (Davis et al. 2015); (Dunne et al. 2012); (Martin et al. 2014); (Monticone et al. 2012); (Monticone et al. 2013); (Monticone et al. 2014); (Nicholas et al. 2013); (Sleptsova et al. 2013); (Vibe Fersum et al. 2013); Zachariades, 2012)
Brief Pain Inventory	10	(Archer et al. 2016); (Broderick et al. 2014); (Chiauzzi et al. 2010); (Dear et al. 2013); (Dear et al. 2015); (Friesen et al., 2017); (Garcia et al. 2015); (Tang et al. 2012); (Thorn et al. 2011); (Williams et al. 2010)
Multidimensional Pain Index	7	(Andersson et al. 2012); (Buhrman et al. 2011); (Buhrman et al. 2013); Buhrman et al. 2015); (Jungquist et al. 2010); (Otis et al. 2013); (Pigeon et al. 2012)
McGill Pain Questionnaire	3	(Ferrando et al. 2012); (Martínez et al. 2014); (Naylor et al. 2010)
Chronic Pain Grade Questionnaire	3	(Bair et al. 2015); (Heutink et al. 2012; (McBeth et al. 2012)

Note: This table is Electronic Supplementary Table 5 from Knoerl, Smith, & Weisburg (2015).

Figure 3

Search Flow Chart



Note: This figure is Electronic Supplementary Figure 1 in the original article by Knoerl, Smith, & Weisberg (2015).

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CHAPTER IV

SELF-GUIDED ONLINE COGNITIVE BEHAVIORAL STRATEGIES FOR CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY: A MULTICENTER, RANDOMIZED, WAIT-LIST CONTROLLED TRIAL

Abstract

Purpose: To examine the efficacy of a self-guided online cognitive and behaviorally-based pain management intervention called Proactive Self-Management Program for Effects of Cancer Treatment (*PROSPECT)* to reduce "worst" pain intensity for individuals with chronic painful chemotherapy-induced peripheral neuropathy (CIPN). The secondary outcomes were "average" pain intensity, non-painful CIPN symptom severity (numbness and tingling), global impression of change, and pain interference.

Patients and Methods: Sixty patients with chronic painful CIPN were randomized in a 1:1 ratio to receive either eight weeks of self-guided *PROSPECT* or treatment as usual. A seven-day electronic worst pain intensity diary and standardized measures of pain interference, non-painful CIPN symptom severity, global impression of change, and average pain intensity were administered at the baseline and week eight time points. Week eight mean scores evaluated between groups using ANCOVA adjusting for baseline scores.

Results: Individuals (n = 19) who received the *PROSPECT* intervention had a "worst pain" mean change score of -0.94 (SD = 1.36, *Range* = -3.29 – 1.29), while individuals (n = 19) in the control group had a mean change score of 0 (SD = 1.31, *Range* = -3.43–2.86) (p = 0.046; d = 0.54). There were no significant differences in mean change scores between groups for the secondary outcomes.

Conclusion: Use of *PROSPECT* significantly improved worst pain intensity in individuals with chronic painful CIPN, however, there were no significant improvements in any secondary outcome. A larger, adequately powered study testing the *PROSPECT* intervention is needed to determine if improvements in pain may be sustained, evaluate the effect of the intervention on the secondary outcomes, and identify mediators of pain-intensity-related improvement.

Background

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer treatment that can occur in up to 64% of individuals receiving neurotoxic chemotherapy (e.g. platinums, bortezomib, and taxanes) (Cavaletti et al., 2013; Kautio, Haanpaa, Kautiainen, Kalso, & Saarto, 2011; Seretny et al., 2014). The symptoms of CIPN include numbness, tingling, and pain in the extremities, which can persist months to years following the completion of chemotherapy (Saif & Reardon, 2005; Smith et al., 2014). In about 40% of patients, CIPN becomes chronically painful (Kautio et al., 2011; Loprinzi et al., 2011; Smith, Cohen, Pett, & Beck, 2010). Patients with painful CIPN often report decreases in quality of life and physical function and may be required to stop potentially lifesaving neurotoxic chemotherapy regimens (Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014; Stubblefield et al., 2009).

Despite the known negative effects that painful CIPN has on physical function and quality of life, there are few effective treatments for painful CIPN. Duloxetine 60 mg/day is

currently the only medication recommended for the treatment of painful CIPN (Hershman et al., 2014; E. M. Smith et al., 2013). Due to their efficacy in other neuropathic pain populations, antidepressants and anticonvulsants are often used to treat painful CIPN (Hershman et al., 2014). However, adherence to these types of medications is poor due to side effects or lack of efficacy (Gharibian, Polzin, & Rho, 2013). Use of an effective, non-pharmacologic intervention for painful CIPN may decrease the need for drug therapy – potentially reducing the overall side effect burden for cancer survivors or create a synergistic pain-reducing effect by the use of multiple modalities. Thus, multi-modal management approaches that incorporate non-pharmacologic approaches for painful CIPN warrant further study.

One non-pharmacologic treatment used commonly for the treatment of chronic pain (e.g. back/neck, musculoskeletal, and fibromyalgia) is therapist administered cognitive behavioral pain management (Christiansen, Oettingen, Dahme, & Klinger, 2010; McBeth et al., 2012; Otis et al., 2013; Thorn et al., 2011; Williams, Eccleston, & Morley, 2012). This intervention is designed to help patients self-manage pain and co-occurring symptoms such as anxiety, depression, and insomnia through cognitive and behavioral strategies such as relaxation, behavioral sleep strategies, activity pacing, and cognitive restructuring (Ehde, Dillworth, & Turner, 2014; Kerns, Sellinger, & Goodin, 2011). Cognitive behavioral pain management may improve pain intensity by inducing structural changes in the prefrontal cortex (e.g., increased gray matter volume). This may provide individuals with increased executive control function and subsequently, a greater ability to reappraise and gain a greater sense of control over their pain. Structural changes in the prefrontal cortex then may lead to the release of neurotransmitters (e.g., norepinephrine and serotonin) that influence descending pain inhibition mechanisms (Jensen et al., 2012; Seminowicz et al., 2013). Barriers related to the delivery of therapist administered

cognitive behavioral pain management in practice include 1) lack of access to a reputable therapist, 2) cost associated with treatment, 3) negative stigma associated with psychological therapies, and 4) transportation to the clinic (Ehde et al., 2014; Knoerl et al., 2015). One way to overcome these barriers is to offer this treatment in a self-guided format. A self-guided cognitive behavioral pain management intervention provides patients with access to symptom management strategies that they can practice at their own pace without the need to travel to meet with a therapist. There is strong evidence supporting the efficacy of self-guided cognitive behavioral pain management for chronic pain (Dear et al., 2013; Knoerl et al., 2015; Macea, Gajos, Daglia Calil, & Fregni, 2010; Williams et al., 2010). However, little is known about the efficacy of self-guided cognitive behavioral pain management for chronic painful CIPN.

Purpose

The purpose of this randomized, waitlist-control pilot study was to test the efficacy of a self-guided online cognitive and behaviorally-based pain management intervention called Proactive Self-Management Program for Effects of Cancer Treatment (*PROSPECT)* to reduce worst pain intensity for individuals with chronic painful CIPN in comparison to individuals receiving treatment as usual (Aim 1). Secondarily, we explored the efficacy of the *PROSPECT* intervention to improve non-painful CIPN symptom severity (e.g., numbness and tingling), pain interference, average pain severity, and patients' perceived global impression of change (Aim 2). Lastly, we explored participant acceptability of and satisfaction with *PROSPECT* (Aim 4).

Methods

Setting and Sample

Sixty patients were recruited from five outpatient community and/or academic oncology clinics from May 1, 2016 to October 4, 2016. Patients were eligible if they 1) were over 25 years

of age, 2) self-reported 4/10 worst CIPN pain that persisted three months or longer following the cessation of neurotoxic chemotherapy, 3) had at least National Cancer Institute Common Terminology Criteria for Adverse Events grade one sensory peripheral neuropathy (National Cancer Institute, 2010), 4) had a stable analgesic medication regimen (≤ 10% change in dosage in the two weeks prior to study enrollment), and 5) were able to access/use a computer. Participants were excluded if they had 1) a prognosis of less than three months, 2) peripheral neuropathy due to other causes, 3) planned to receive neurotoxic chemotherapy while enrolled in the study, or 4) participated in cognitive behavioral pain management in the past. This study was approved by the Institutional Review Board associated with each study site and written informed consent was obtained from all enrolled participants.

Treatment Groups

Participants were randomly assigned following simple randomization procedures to either eight weeks of *PROSPECT* or treatment as usual (control) in a 1:1 ratio using a computer generated random numbers table. Randomization was stratified by recruitment site to balance out center effects. The principal investigator generated the random allocation sequence, enrolled the patients, and assigned participants to a study group. The computer generated random numbers table was stored on a spreadsheet. The principal investigator did not view the spreadsheet until informed consent was obtained and all baseline assessments were completed by the participant. Following informed consent and completion of all baseline assessments, participants were informed of their study group assignment. Following the administration of the baseline assessments by the principal investigator, trained study staff administered all data collection procedures at the subsequent time points.

PROSPECT. The password-protected *PROSPECT* website contained cognitive behavioral pain management strategies and information designed to help individuals manage pain and co-occurring symptoms following cancer treatment (e.g., anxiety, depression, sleep, fatigue, and impaired cognition) (Eckhoff, Knoop, Jensen, & Ewertz, 2015; Moriarty, McGuire, & Finn, 2011; Tang, Wright, & Salkovskis, 2007; Taylor et al., 2007). Content (10 modules; Table 6) is presented using both written and video formats, and patients can download worksheets further describing the strategies. At baseline, participants were trained on how to navigate the *PROSPECT* website and were encouraged to complete the "Steps for Me" link, which recommends modules based on the patient's responses to questions about symptom severity and symptom management practices. Participants did not receive any additional encouragement from the study staff after obtaining access to the *PROSPECT* website.

Control. Participants in both groups continued to receive their usual care from their primary provider. Participants randomized to the control group received access to the *PROSPECT* website at the end of the study.

Measures

An 11 – point numerical rating scale (NRS) of pain intensity was used to measure worst and average CIPN pain severity (0, no pain; 10 pain as bad as you can imagine) (Cleeland & Ryan, 1994; Dworkin et al., 2005). The 11 – point worst CIPN pain NRS was administered over seven consecutive days at the baseline and week eight time points. The 11-point NRS is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin et al., 2005) and several trials have supported its reliability and validity (Hjermstad et al., 2011; Jensen, Karoly, & Braver, 1986; Li, Liu, & Herr, 2007). Based on evidence suggesting that worst pain intensity is more highly correlated with average

functional interference ($r = 0.65$) than average ($r = 0.58$) or current ($r = 0.35$) pain intensity (Harris, Li, Flynn, & Chow, 2007; Shi, Wang, Mendoza, Pandya, & Cleeland, 2009), worst pain intensity was selected as the primary outcome.

Several other co-morbid symptoms were assessed as recommended by IMMPACT to increase our ability to compare the results of this study with other trials testing interventions for chronic pain. The Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference 4a (four items; 1, not at all; 5, very much; transformed total score range 41.6-75.6) subscale measures the effect of pain on the social, cognitive, and physical aspects of one's life over the past seven days (National Institute of Health Patient-Reported Outcomes Measurement Information System, 2014). There is strong evidence supporting the reliability and validity of the PROMIS pain interference item bank (Amtmann et al., 2010). Depression, fatigue, sleep-related impairment, and anxiety were also measured using PROMIS instruments and the findings are reported in Chapter Five of this Dissertation document. In addition, we used the Patient Global Impression of Change (PGIC) to assess patients' subjective impression of improvement/worsening over the course of treatment. The PGIC is a self-report item designed to assess patients' overall impression of improvement over the course of a clinical trial (Guy, Psychoparhmacology Research Branch, & Early Clinical Drug Evaluation Program, 1976). The seven-point scale ranges from "very much worse" to "very much improved" (Guy et al., 1976).

The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy Scale (QLQ-CIPN-20) measures patient's symptoms and functional limitations related to CIPN in sensory, motor, and autonomic function domains (20 items; 1, not at all; 4, very much) (Postma et al., 2005). The responses from each respective scale are then transformed and scored from 0 – 100, with higher scores

representing worsening symptom (Postma et al., 2005). The internal consistency reliability alpha coefficient has been reported as 0.88, 0.88, and 0.78 for the sensory, motor, and autonomic subscales, respectively (Lavoie Smith et al., 2013). Further evidence demonstrates that the sensory and motor subscales are moderately-highly responsive to change (Cohen's $d = 0.82$ and 0.48, respectively) (Lavoie Smith et al., 2013).

We adapted questions from the Acceptability E-Scale to assess participant acceptability of and satisfaction with the *PROSPECT* website (Berry et al., 2011; Tariman, Berry, Halpenny, Wolpin, & Schepp, 2011). The questionnaire contains seven items that are scored on a 1 – 5 scale, with higher scores representing greater acceptability and satisfaction. Survey questions ask participants how much they enjoyed using *PROSPECT* and how helpful the modules were in improving their symptoms.

Participants completed a demographic survey (i.e., sex, age, race, ethnicity, employment status, marital status, education, previous computer use) prior to the completion of the baseline assessments. Study staff abstracted participant cancer diagnosis (i.e., disease and stage) and treatment (e.g., chemotherapy type), medication dosage, and comorbid condition-related information from the patients' electronic medical records.

Study Procedures

Baseline. Following informed consent, participants completed the baseline assessments (11- point worst and average CIPN pain NRS, PROMIS Pain Interference 4a, QLQ-CIPN20, demographics) via computer tablet. Participants were then notified of their study group assignment and emailed the seven-day worst pain diary. After completing the pain diary, the participants were emailed the *PROSPECT* website link and password, or instructions about the

control group. Also at baseline, study staff abstracted cancer diagnosis/treatment and medication dosage-related information from the patients' electronic medical records.

Week four and eight time points. Survey links to the same battery of assessments administered at baseline were emailed to participants four and eight weeks after randomization. At these same time points, participants were contacted by telephone as a reminder to complete the electronic surveys and to answer structured interview questions about changes in medication dosage/frequency. Unique to the week eight-time point, participants in both groups completed the PGIC and individuals in the intervention group completed the Adapted Acceptability E-Scale and were contacted by telephone to discuss the most positive and negative aspects of *PROSPECT*. Participants were also emailed a survey each week inquiring about the number of minutes spent using *PROSPECT* or other symptom management resources. At the end of the study, control group participants were emailed the link to the *PROSPECT* website.

Statistical Analyses

All data was analyzed using R version 3.3.2 (R Development Core Team, 2017). Descriptive statistics of the centrality and dispersion of all survey data and demographic data were calculated. All analyses were calculated based on the total number of individuals that completed the baseline and week eight outcome measures. Due to the pilot nature of this study, power analyses were not conducted for any aim.

Aim 1. We averaged patient's responses from the seven-day worst CIPN pain diary for the baseline and week eight time points. Participants must have completed five out of the seven daily worst pain ratings at the baseline and week eight time points to be included in the analysis (Heapy et al., 2016). Week eight mean scores in worst CIPN pain intensity (0 – 10 NRS diary) were compared between groups using ANCOVA adjusting for baseline scores and age.

Aim 2. Week eight mean scores in CIPN symptom severity (QLQ-CIPN-20 sensory and motor subscales), average pain (average CIPN pain NRS), and pain interference (PROMIS Pain Interference 4a) were compared between groups using ANCOVA adjusting for baseline and age. Fisher's exact test was used to analyze proportional differences between those who experienced "improvement" (PGIC score ≥ 5) and "no improvement" (PGIC score ≤ 4) in the two study arms.

Aim 4. Descriptive statistics for the items of the Adapted Acceptability E – Scale were calculated. Additionally, we summarized responses from the semi-structured telephone interviews to determine the most positive and negative aspects of *PROSPECT* and the biggest barriers to accessing and using the strategies contained within *PROSPECT*.

Results

Patients

A review of the study sites' electronic medical records revealed 288 potentially eligible participants (Figure 4 CONSORT Flow Diagram). Following telephone screening procedures, 215 patients were deemed ineligible based upon inclusion/exclusion criteria and 13 declined to participate. Sixty participants were randomized to the *PROSPECT* intervention ($n = 30$) or treatment as usual control ($n = 30$) groups. After randomization, thirteen participants terminated the study early due to personal reasons (e.g., lack of time) or were lost to follow up. Participants who terminated the study early did not complete any outcome measurements beyond the baseline time point. The attrition rate for the study was 22%. Overall, 23 and 24 participants were eligible for analysis in the *PROSPECT* and control arms.

Patient characteristics are described in Table 7. Individuals in the *PROSPECT* group had higher levels of fatigue and sleep-related impairment in comparison to individuals in the control group, otherwise, there were no differences. When comparing protocol completers vs. non-

completers, non-completers had a greater percentage of individuals with stage IV cancer (46%) than completers (19%), but, baseline pain and co-occurring symptom severity did not differ.

Aim 1

Individuals with chronic painful CIPN who received the eight-week *PROSPECT* intervention had a mean change score of -0.94 (*SD* = 1.36, *Range* = -3.29 – 1.29, *CI* = -1.6, -0.28), while individuals in the treatment as usual control group had a mean change score of 0 in worst pain intensity (*SD* = 1.31, *Range* = -3.43 – 2.86, *CI* = -0.63, 0.63) (Table 8; Figures 5 - 6). The difference in week eight worst CIPN pain intensity mean scores between groups was significant when adjusting for baseline scores alone (*B* = -0.91; *p* = 0.046; *CI* = -1.79, -0.02; *d* = 0.54) (*n* = 38). When adjusting for age and baseline scores, the difference in week eight worst CIPN pain intensity mean scores between groups trended towards significance (*B* = -0.91; *p* = 0.058; *CI* = -1.86, 0.03; *d* = 0.52) (*n* = 38). Three participants receiving *PROSPECT* and one participant receiving treatment as usual experienced a clinically significant (>30%) reduction in worst CIPN pain intensity (Figure 7) (Farrar, Young Jr, LaMoreaux, Werth, & Poole, 2001).

Aim 2

There were no significant differences in mean change scores for average pain, pain interference, or non-painful CIPN symptoms (e.g., numbness and tingling) (Table 8; Figure 5). Trends in average pain scores and pain interference (Figures 8 – 9) across time also indicated that *PROSPECT* provided no clear benefit over usual care. However, trends in non-painful CIPN symptoms suggested that individuals receiving *PROSPECT* were experiencing considerable improvements as the study progressed (Figure 10). There was also a greater number of individuals in the *PROSPECT* group reporting improved impression of change following the

completion of the trial, but, the difference between groups was not significant (Table 8; Figure 11).

Aim 4

Overall, acceptability and satisfaction with the study and *PROSPECT* website was moderate to high, with mean Adapted Acceptability E-Scale item scores ranging from 3.26 to 4.58/5 (Table 9). Participants reported that ease of use, the ability to print off work sheets based upon the strategies they learned, and having access to many relevant pain symptom management strategies were all positive aspects of the *PROSPECT* intervention. Conversely, participants thought that there were not enough information and/or strategies to help manage the symptoms of non-painful neuropathy (e.g., numbness and tingling). Participants also cited lack of time and difficulty changing symptom management practices as barriers to implementing the strategies they learned. Lastly, participants thought that *PROSPECT* would have been more beneficial if it contained cognitive strategies related to pain management, features to interact with medical professionals to review strategies and symptoms, or was provided in the beginning stages of cancer treatment as they were beginning to experience painful CIPN symptoms.

Adherence

In terms of adherence, the mean number of minutes individuals (*n* range six – 18) in the intervention group spent using *PROSPECT* and other symptom management resources (e.g., physical therapy, meditation, pool therapy, massage) was highest at the beginning of the study and declined as the study progressed. The average amount of time participants (*n* range six – 21) in the control group spent using symptom management strategies (e.g., ice therapy, massage, stretching, yoga, distraction, exercise) varied across the eight-week study period (Table 10). In terms of medication changes, there was a greater number of individuals in the *PROSPECT* group

that increased pain medication frequency/dose not indicated for CIPN pain management (Hershman et al., 2014), but otherwise, there were no considerable differences in the number of participants changing medication frequency/dose between groups (Figure 12).

Discussion

This eight week, randomized-controlled pilot trial demonstrated that a self-guided online cognitive and behaviorally-based pain management intervention—*PROSPECT*—significantly improved worst pain intensity in individuals with chronic painful CIPN. Further, there were no significant differences in mean change scores between groups for the secondary outcomes of pain interference, non-painful CIPN symptoms, average pain, or global impression of change.

Individuals with chronic painful CIPN interacting with the eight-week PROSPECT intervention reported a mean decrease in worst pain intensity of 0.94. The mean decrease in pain intensity found in this current study is comparable to the effect of duloxetine, the only pharmacological agent currently recommended for the treatment of chronic painful CIPN (Hershman et al., 2014). The authors of a randomized, crossover, placebo-controlled study found that use of duloxetine 60 mg/day resulted in a mean decrease of 1.06 on a 0 – 10 NRS of average pain in individuals with chronic painful CIPN ($p = 0.003$; $d = 0.513$) (Smith et al., 2013). On the contrary, *PROSPECT* had no effect on the secondary outcome of average pain intensity in this current study. The comparison between average pain mean change scores between studies is challenging because Smith et al. assessed average pain over the past 24 hours, not seven days (Shi et al., 2009; Smith et al., 2013). Nevertheless, the reported effect sizes and mean changes for the two studies' primary outcomes were similar for *PROSPECT* and duloxetine.

Despite statistically significant improvements in worst CIPN pain intensity following *PROSPECT* use, the findings were not clinically significant. Clinically significant improvements

in pain intensity represent a 30% reduction in pain (Farrar, Young Jr, LaMoreaux, Werth, & Poole, 2001). The overall worst CIPN pain intensity mean change score for individuals receiving *PROSPECT* was -0.94 and only three individuals reported a greater than 30% reduction in pain. Further, while there was a greater number of individuals reporting perceived overall improvement following *PROSPECT* than following usual care alone, there were no significant differences between groups. This may be explained by the low number of individuals reporting a clinically significant reduction in worst pain intensity or that individuals were more distressed by co-occurring symptoms, which *PROSPECT* may not have adequately addressed. Overall, while *PROSPECT* significantly improved worst CIPN pain intensity, the results must be interpreted with caution due to the small sample size and lack of a placebo control group, clinically significant pain intensity improvement, and an intent-to-treat analysis.

There have been no published studies reporting the effects of cognitive behavioral pain management for non-painful CIPN symptoms (e.g., numbness and tingling in the periphery). While non-painful CIPN symptoms such as numbness and tingling are a result of peripheral nervous system damage (e.g. dorsal root ganglia of primary sensory neurons) (Carozzi, Canta, & Chiorazzi, 2015; Park et al., 2013), non-painful CIPN symptoms are still associated with changes in the central nervous system. For example, a study by Nudelman et al. (2016) demonstrated that increased CIPN symptoms one month post neurotoxic chemotherapy are associated with changes in perfusion in brain areas associated with nociceptive processing (e.g., anterior cingulate cortex and frontal gyrus). Thus, interventions that target centrally-mediated mechanisms such as cognitive behavioral pain management, may also be efficacious for the treatment of non-painful CIPN symptoms (Jensen et al., 2012; Seminowicz et al., 2013). The results of this current study support this conclusion as individuals receiving *PROSPECT* had greater improvements in non-

painful CIPN symptoms over the eight-week trial period than individuals receiving usual care, but, the difference was not significant. Further research is needed to determine if interventions targeting centrally-mediated mechanisms (e.g., cognitive behavioral pain management) can also influence non-painful CIPN symptoms.

There were no significant differences in pain interference between groups. While physical function and seven-day recall of worst pain intensity are moderately-strongly correlated ($r = 0.65$) (Shi et al., 2009), self-guided cognitive behavioral pain management interventions are most effective when targeting a specific outcome (Knoerl et al., 2015). Therefore, perhaps if the *PROSPECT* intervention was tailored to include more physical activity training and educational resources, it would have had a greater impact on pain interference. Further, while there was a greater number of individuals reporting perceived overall improvement following *PROSPECT* than following usual care alone, there were no significant differences between groups. This may be explained by the low number of individuals reporting a clinically significant reduction in worst pain intensity or that individuals were more distressed by non-painful symptoms (e.g., numbness and tingling), which *PROSPECT* may not have adequately addressed.

Based on trends in *PROSPECT* usage and worst pain intensity improvement, the results suggest that participants interacted with the website frequently at first to learn and practice the strategies, but then could incorporate the strategies into their day-to-day activities to improve pain intensity independent of logging in to *PROSPECT*. However, little is known about the optimal dose of *PROSPECT* because we did not actively monitor patient's usage (e.g., electronic tracking) and the response rate to the self-report measures was low. Significant predictors of adherence to self-management interventions include providing guidance/support, ample amount of time to use the intervention, and high satisfaction with intervention content (Beatty &

Binnion, 2016). Thus, adherence to *PROSPECT* may be bolstered in future studies if 1) participants have an opportunity to interact with a health care professional (e.g., weekly video or telephone call with nurses) (Heutink et al., 2012; Jungquist et al., 2010) to discuss pain-related symptoms and strategy use, 2) participants have more time to interact with the strategies of *PROSPECT* (e.g., longer duration, scheduled time to interact with modules, and 3) additional interactive features within *PROSPECT* are designed (e.g., achievement badges, message boards/support groups, visually appealing) (Beatty & Binnion, 2016; Ludden, van Rompay, Kelders, & van Gemert-Pijnen, 2015). Improving adherence to self-guided cognitive behavioral pain management interventions in future research is critical to establish an optimal dose that can be prescribed in the clinical setting and to compare results across trials.

One common limitation of recent placebo-controlled randomized controlled trials testing interventions for individuals with chronic pain is high placebo response (Dworkin et al., 2012; Dworkin et al., 2011, 2013; Katz, 2005). While this study did not contain a placebo control, psycho-educational interventions are prone to non-specific effects (e.g. study staff-participant interaction, participant motivation for participation, lack of blinding, credibility of treatment) that may have accounted for the efficacy of the intervention (Donovan, Kwekkeboom, Rosenzweig, & Ward, 2009). We attempted to minimize non-specific effects in this current trial by implementing strategies to improve assay sensitivity, or the ability to distinguish an effective treatment from an ineffective treatment (Dworkin et al., 2012). Strategies used to increase the assay sensitivity of this trial design included 1) baseline participant 4/10 or greater worst CIPN pain intensity, participant pain duration of at least three months since completion of chemotherapy, 3) flexible intervention dosing, 4) standardized data collection procedures for both groups, 5) less than three treatment arms, and 6) small sample size (Dworkin et al., 2012;

Dworkin et al., 2013). The efficacy of these strategies in improving the assay sensitivity of this trial may be evidenced by the lack of control group improvement in worst pain intensity from the baseline to week eight time point. However, an alternate explanation for this finding is that control group participants were not blinded to the intervention they were receiving and thus, knew they were not receiving the intervention. Nevertheless, future studies should continue to implement strategies to improve assay sensitivity to facilitate the identification of effective treatments for individuals with chronic pain.

There are several limitations to this current study. First, the dropout rate in this study was approximately 22%. This dropout rate is consistent with other self-guided cognitive behavioral pain management intervention studies (Macea et al., 2010) and the demographic characteristics of the completers and non-completers were similar between groups. Yet, due to the high number of individuals with stage IV cancers dropping out of the study, further research is needed to examine the feasibility of administering *PROSPECT* in individuals with advanced cancer. Second, this was a pilot study and as such, was not powered to detect differences in the primary or secondary outcomes. Third, while worst pain intensity improved following *PROSPECT* use, little is known as to what components led to these improvements. The identification of mediators of pain intensity improvement may allow for the development of self-guided cognitive behavioral pain management interventions containing the strategies hypothesized to improve the mediators. Fourth, higher pain medication and other symptom management activity use by individuals in *PROSEPCT* may have confounded the results of the primary outcome. Fifth, we cannot generalize the results of this study to individuals with CIPN resulting from a specific neurotoxic agent because we examined the *PROSPECT* intervention in individuals who received varying types of neurotoxic drugs. Lastly, individuals receiving *PROSPECT* had higher levels of

baseline fatigue and sleep-related impairment than individuals in the control group. Despite these differences in co-occurring symptom severity at baseline, individuals receiving *PROSPECT* still experienced greater reductions in worst CIPN pain intensity.

Overall, currently there is one recommended pharmacological agent and no non-pharmacological modalities recommended for the treatment of chronic painful CIPN. This pilot study provides preliminary evidence supporting the efficacy of a self-guided online cognitive and behaviorally-based pain management intervention for improving worst pain intensity in individuals with chronic painful CIPN. However, due to the small sample size and stated limitations, a larger study is needed to determine the true effect of *PROSPECT* on pain intensity and the secondary outcomes. If shown to be efficacious in a larger study, *PROSPECT* should be tested alongside pharmacological agents for the treatment of chronic painful CIPN. Because pain often clusters with other symptoms (Miaskowski et al., 2014; Smith et al., 2015), multi-modal treatment approaches for chronic pain are beneficial because they target both underlying pain and pain-related physiological mechanisms.

Table 6

Summary of Proactive Self-Management Program for Effects of Cancer Treatment Modules

Modules	Content
About Late Effects	Education about common cancer treatment – related side effects (i.e., pain, fatigue, problems with memory, emotional distress, sleep problems)
Talk to Your Team	Strategies to promote communication between the patient and their provider regarding cancer treatment-related symptoms
Get Your Body Moving	Outlines the benefits of physical activity during cancer treatment and provides strategies to start and maintain regular physical activity
Get a Better Night's Sleep	Sleep hygiene strategies to help individuals fall and stay asleep at night
Slow Your Body Down	Provides step-by-step instructions for various relaxation techniques (i.e., deep breathing, guided imagery, progressive muscle relaxation)
Improve Your Thinking	Strategies to combat memory and thinking problems.
Set Some Goals	Strategies to set realistic goals and carry out planned goals.
Don't Over Do It	Activity pacing strategies
Time for You	Details strategies to overcome barriers and challenges related to taking time out of the day to participate in enjoyable activities to renew the mind and body.
About Peripheral Neuropathy	Information about the symptoms of peripheral neuropathy, strategies to treat the symptoms of neuropathy, and safety precautions to take due to the symptoms of neuropathy

Table 7

Demographic, Cancer Treatment, and Medication Use Characteristics of the Recruited Sample at Baseline[a]

Characteristic	PROSPECT (*N* = 30)	Control (*N* = 30)
Sex		
Female	23 (76.7)	22 (73.3)
Male	7 (23.3)	8 (26.7)
Age		
Mean (*SD*)	58.93 (9.33)	63.37 (8.36)
Race		
African American	2 (6.7)	1 (3.3)
White	27 (90)	28 (93.3)
Unknown	1 (3.3)	1 (3.3)
Ethnicity		
Hispanic	0	1 (3.3)
Non-Hispanic	25	22
Unknown	5 (16.7)	7 (23.3)
Education (*n* = 59)		
High School or less	4 (13.3)	6 (20.7)
Some college	13 (43.3)	12 (41.4)
College graduate	8 (26.7)	6 (20.7)
Post graduate degree	5 (16.7)	5 (17.2)
Employment Status		
Employed	13 (43.3)	7 (23.3)
Out of work	3 (10)	2 (6.7)
Homemaker	0	1 (3.3)
Retired	9 (30)	17 (56.7)
Unable to work	5 (16.7)	3 (10)
Marital Status		
Single	2 (6.7)	2 (6.7)
Married	18 (60)	24 (80)
Separated	1 (3.3)	1 (3.3)
Divorced	7 (23.3)	2 (6.7)
Widowed	2 (6.7)	1 (3.3)
Amount of Computer Use		
Once a month	1 (3.3)	6 (20)
About once a week	1 (3.3)	1 (3.3)
More than once a week	28 (93.3)	23 (76.7)
Cancer Stage		
Early I – II	13 (43.3)	9 (30)
III	10 (33.3)	11 (36.7)

Metastatic	6 (20)	9 (30)
Unknown	1 (3.3)	1 (3.3)
Cancer Type		
Breast	13 (43.3)	10 (33.3)
Gastrointestinal	13 (43.3)	13 (43.3)
Genitourinary	0	1 (3.3)
Lung	1 (3.3)	3 (10)
Multiple	1 (3.3)	2 (6.7)
Lymphoma	2 (6.7)	1 (3.3)
Chemotherapy Type		
Platinums	13 (43.3)	13 (43.3)
Taxanes	12 (41.4)	8 (26.7)
Bortezomib	1 (3.3)	0
Vinca Alkaloids	1 (3.3)	2 (6.7)
Multiple	3 (10)	7 (23.3)
Pain-related Symptoms (*Mean*, *SD*)		
Anxiety	54.79 (9.42)	51.58 (7.83)
Depression	52.92 (7.98)	49.51 (7.17)
Fatigue	59.18 (8.26)	52.73 (8.25)
Sleep-related Impairment	58.65 (6.67)	55.07 (6.09)
Comorbid Conditions		
None	12 (40)	7 (23.3)
Chronic Lung Disease	1 (3.3)	1 (3.3)
Coronary Artery Disease	0	2 (6.7)
Diabetes	0	3 (10)
Gastrointestinal Disease	0	2 (6.7)
Chronic Kidney Injury	1 (3.3)	0
Obesity	1 (3.3)	2 (6.7)
Hypertension	12 (40)	14 (46.7)
Anxiety	3 (10)	4 (13.3)
Depression	5 (16.7)	4 (13.3)
Other	11 (36.7)	15 (50)
Baseline Medications		
Neuropathic Pain Medications[b]	9 (30)	6 (20)
Other Analgesics[c]	6 (20)	8 (26.7)
Both Neuropathic Pain Medications and Other Analgesics	9 (30)	8 (26.7)
Anti-anxiety	8 (26.7)	8 (26.7)
Sleep Medications	2 (6.7)	3 (10)
Antidepressants[d]	5 (16.7)	4 (13.3)
Fatigue Medications	0	0

Note:

[a] Data are means (*SD*) or numbers (*%*)

[b] Based upon treatment recommendations for CIPN by Hershman et al. (2010), neuropathic pain medications included: duloxetine, gabapentin, pregabalin, and antidepressants.

[c] Other analgesics included: oxycodone, morphine, ibuprofen, acetaminophen
[d] Three participants (two in control, one in PROSPECT) were receiving nortriptyline, a medication that has shown efficacy to treat pain in other neuropathic pain patient populations.

Table 8

Mean Scores for Primary and Secondary Outcomes from Baseline to Week Eight

Outcomes	Intervention Mean (*SD*)	Control Mean (*SD*)	Intervention Mean Change (*SD*)[b]	Control Mean Change (*SD*)[b]
Worst Pain[a] (*N* = 38)				
Baseline	5.04 (1.24)	4.78 (1.78)	-0.94 (1.36)	0 (1.31)
Week 4	5.42 (2.32)	5.60 (2.5)		
Week 8	4.10 (1.81)	4.78 (1.93)		
Average Pain (*N* = 42)				
Baseline	4.37 (1.89)	3.91 (2.52)	0.21 (2.59)	1.44 (2.87)
Week 8	4.58 (1.87)	5.35 (1.99)		
Pain Interference (*N* = 42)				
Baseline	57.81 (8.16)	57.33 (7.07)	-1.10 (7.58)	-0.89 (8.29)
Week 8	56.72 (7.96)	56.43 (7.74)		
CIPN Sensory (*N* = 42)				
Baseline	49.34 (16.68)	45.99 (20.1)	-8.93 (17.69)	-4.04 (13.57)
Week 8	40.41 (18.66)	41.95 (17.37)		
CIPN Motor (*N* = 42)				
Baseline	34.21 (17.04)	25.83 (18.41)	-7.3 (15.6)	-3.08 (14.37)
Week 8	26.91 (17.71)	22.75 (13.3)		
Impression of Change (*N* = 41)				
8 Weeks (Improved)	9/19 (47.3%)	6/22 (27.3%)	Not Applicable	
8 Weeks (No Change/Worse)	10/19 (52.7%)	16/22 (72.7%)		

Note:

[a] Week 4 data is documented to provide information related to time to response because there was found to be a significant difference in mean change scores ($p < 0.05$) between treatment condition at the week eight time point.

[b] Change scores were calculated by subtracting baseline from week eight subscale scores only in patients who provided baseline and week eight scores.

Table 9

Acceptability and Satisfaction with PROSPECT

Acceptability and Satisfaction – Adapted Acceptability E – Scale (*n* = 19)	Mean	SD	Range
1. How easy was it to access the website on your computer?	4.58	0.84	2 – 5
2. How understandable was the content presented within the website?	4.58	0.69	3 – 5
3. How much did you enjoy using the website?	3.26	1.05	1 – 5
4. How helpful was it to read and participate in the website activities to help manage your symptoms related to CIPN (Pain, physical functioning, anxiety, sleep disturbance, etc.)?	3.36	0.96	1 – 5
5. Was the amount of time it took to complete the activities presented within the website acceptable?	4	1.11	1 – 5
6. Was the amount of time it took to complete the study questionnaires at the baseline, 4 week, and 8-week time points acceptable?	4.42	1.02	1 – 5
7. Overall, how would you rate your satisfaction with the website?	3.95	0.71	3 – 5

Table 10

Mean Number of Weekly Minutes Spent Using PROSPECT and Other Symptom Management Resources by Treatment Group

Week	*PROSPECT* Use*	Symptom Management Use (Intervention)*	Symptom Management Use (Control)*
1	25.4 (0 – 90) (*n* = 14)	67.3 (0 – 390) (*n* = 15)	15.1 (0 – 120) (*n* = 10)
2	12.1 (0 – 60) (*n* = 12)	63.8 (0 – 300) (*n* = 12)	2.5 (0 – 15) (*n* = 6)
3	10 (0 – 20) (*n* = 6)	60 (0 – 210) (*n* = 6)	25 (0 – 160) (*n* = 8)
4	17.1 (0 – 60) (*n* = 14)	19.2 (0 – 140) (*n* = 12)	27.9 (0 – 360) (*n* = 21)
5	5.5 (0 – 30) (*n* = 10)	23 (0 – 180) (*n* = 10)	9.2 (0 – 60) (*n* = 10)
6	16.4 (0 – 72) (*n* = 13)	49 (0 – 420) (*n* = 13)	2.7 (0 – 25) (*n* = 15)
7	7.5 (0 – 35) (*n* = 13)	26.7 (0 – 120) (*n* = 13)	8.1 (0 – 45) (*n* = 12)
8	8.6 (0 – 30) (*n* = 18)	6.7 (0 – 30) (*n* = 17)	32.1 (0 – 495) (*n* = 21)

Note: Symptom management use in the *PROSPECT* group refers to pain management strategies (e.g., physical therapy, meditation, pool therapy, massage) used in addition to the strategies embedded within the *PROSPECT* website, whereas symptom management use in the control group refers to strategies used by participants to manage pain during the study (e.g., ice therapy, massage, stretching, yoga, distraction, exercise).

* Mean number of minutes (*Range)*

Figure 4

CONSORT Flow Diagram

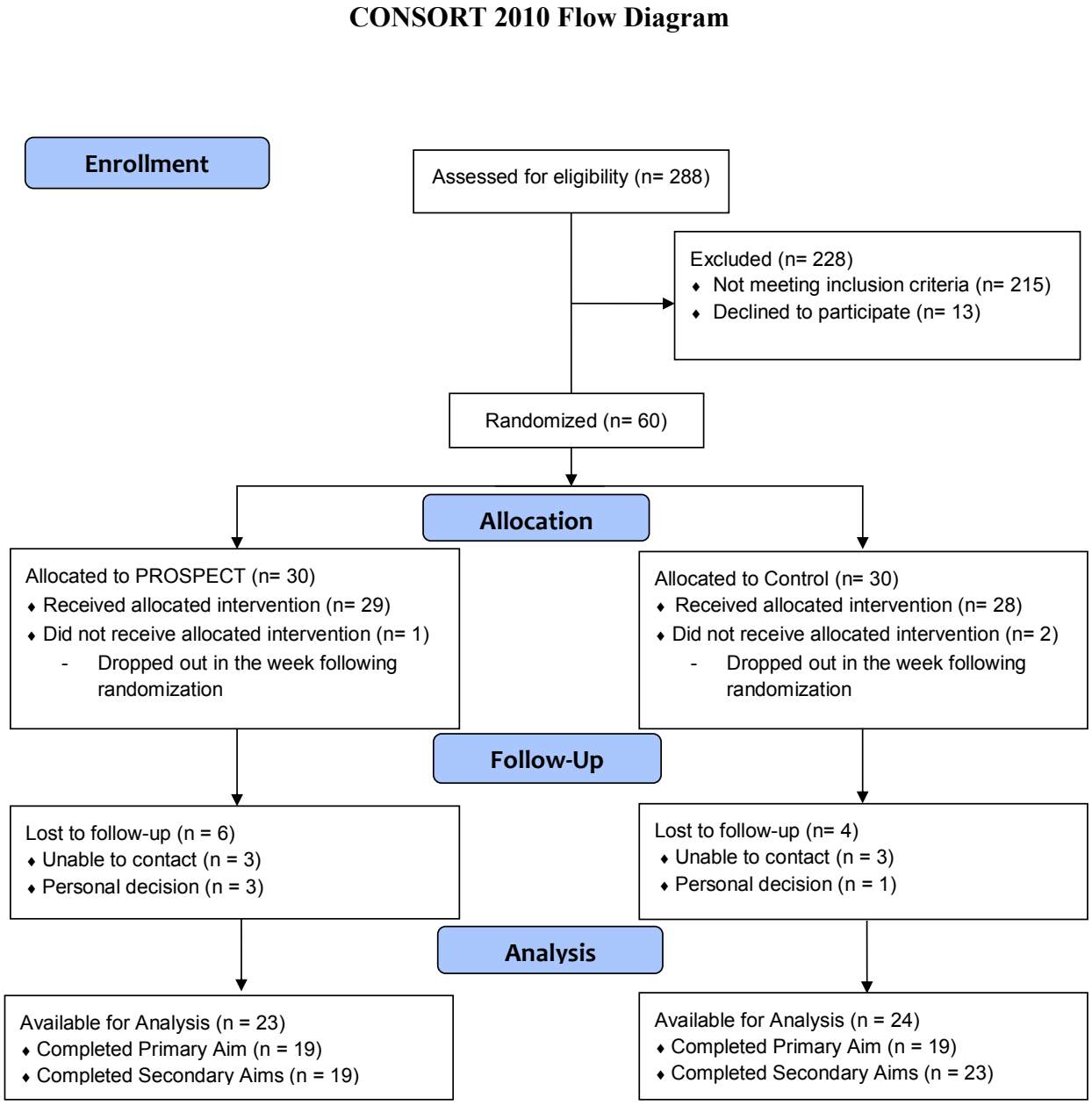


Figure 5

Mean Change Scores of Primary and Secondary Outcomes by Treatment Group

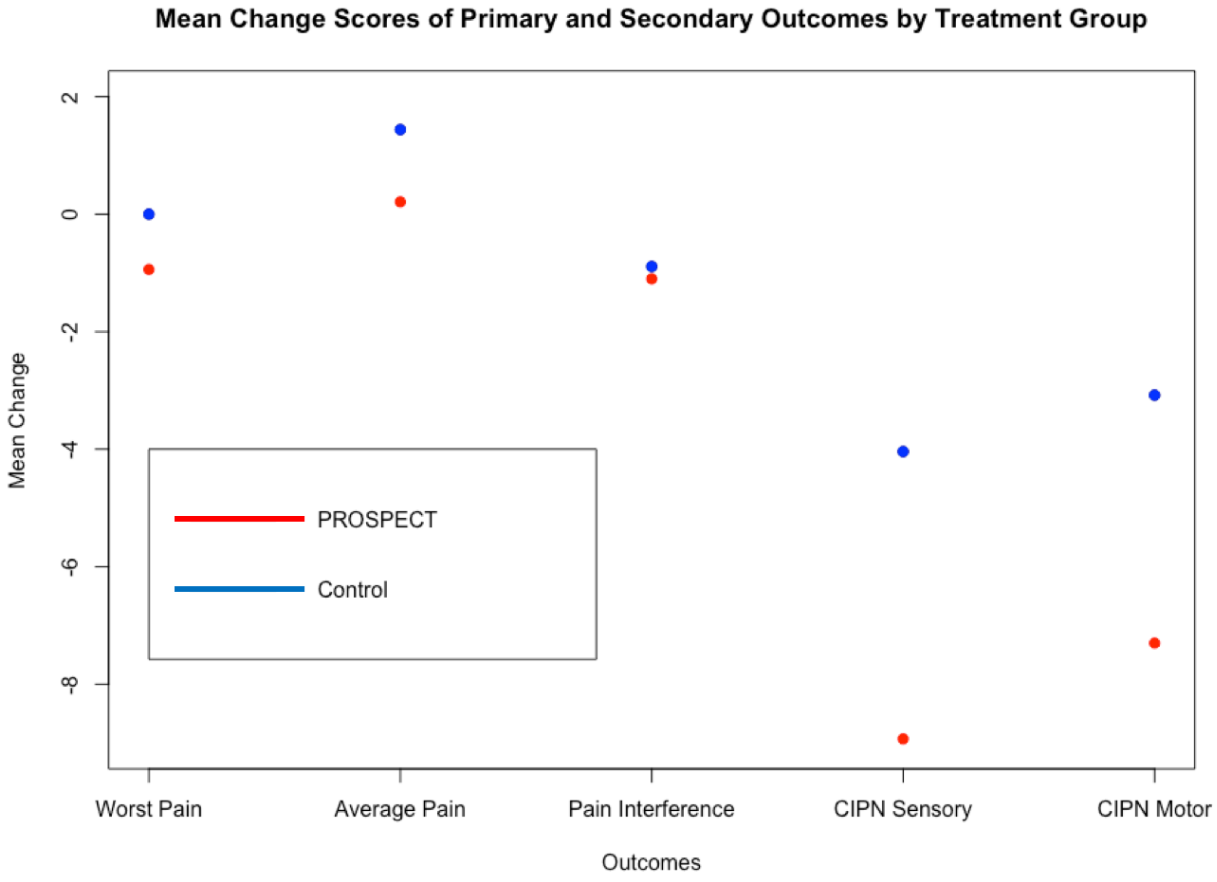


Figure 6

Effect of Treatment Group on Worst CIPN Pain Intensity

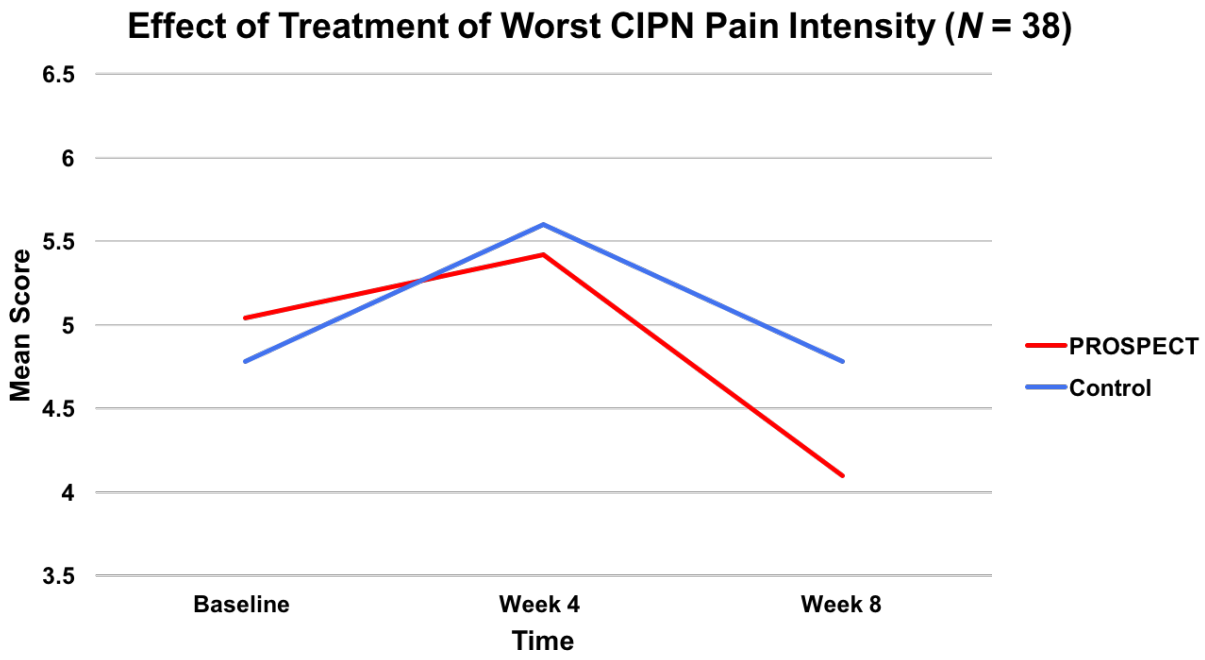


Figure 7

Percent Decrease in Worst Pain Intensity Due to PROSPECT or Treatment as Usual

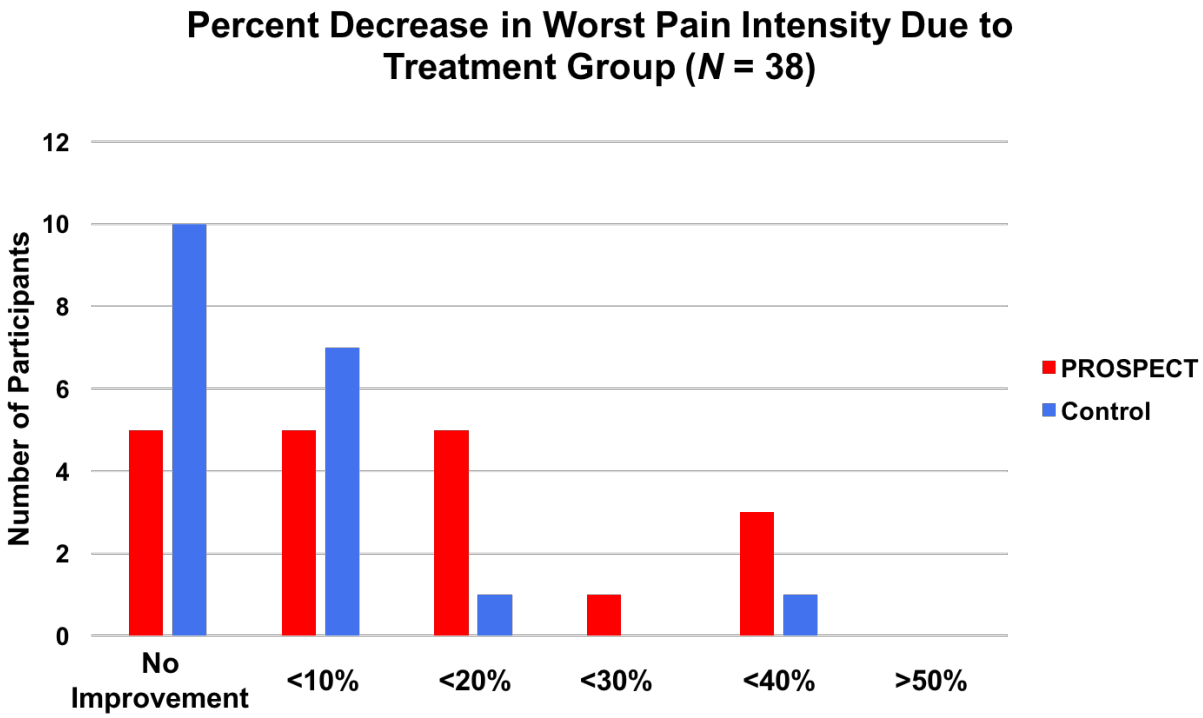


Figure 8

Effect of Treatment Group on Average CIPN Pain Intensity

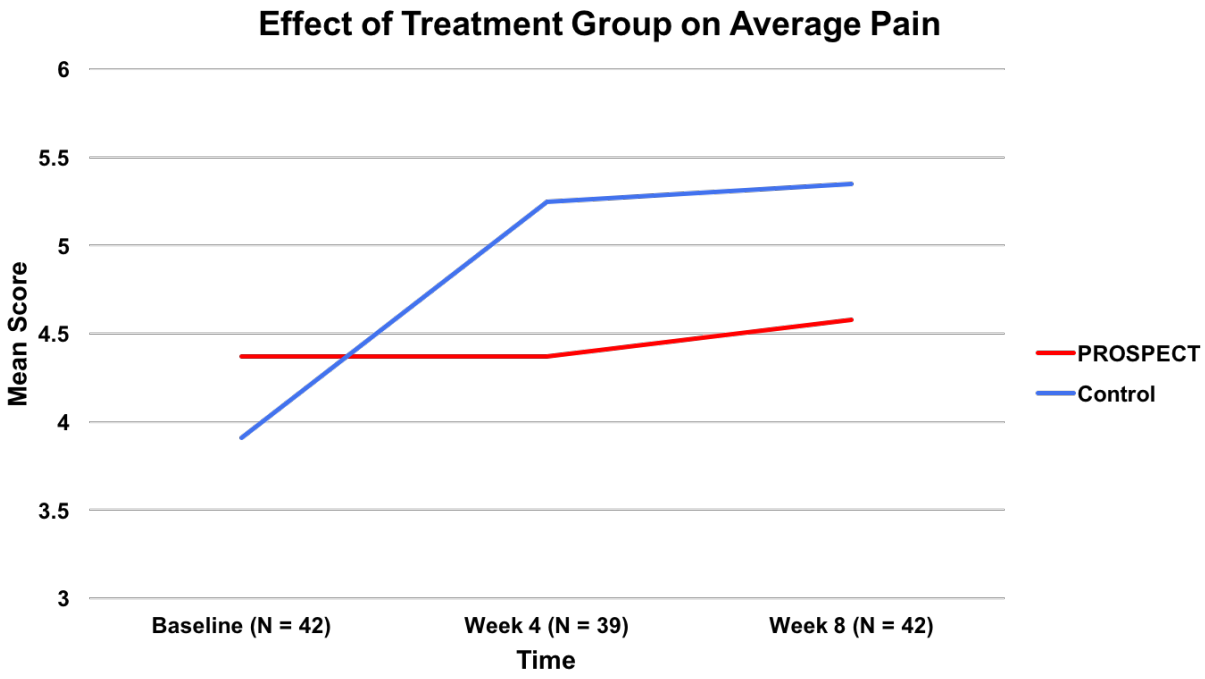


Figure 9

Effect of Treatment Group on Pain Interference

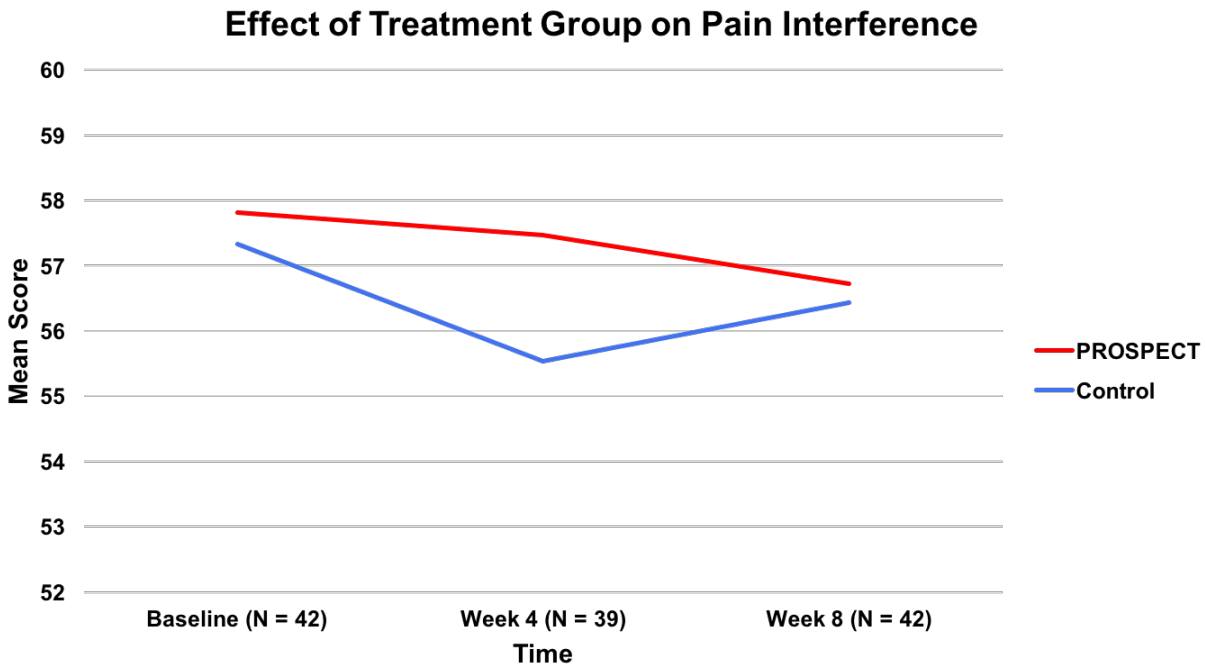


Figure 10

Effect of Treatment Group on Non-Painful CIPN Symptoms

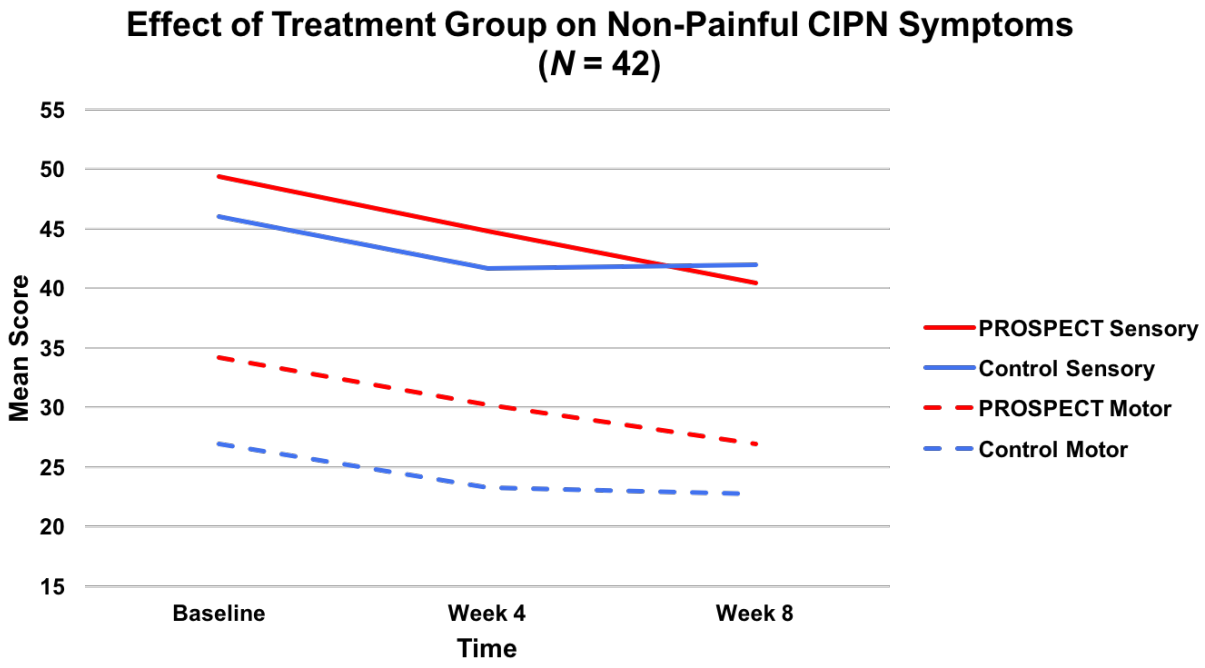


Figure 11

Effect of Treatment on Patient Global Impression of Change Scores

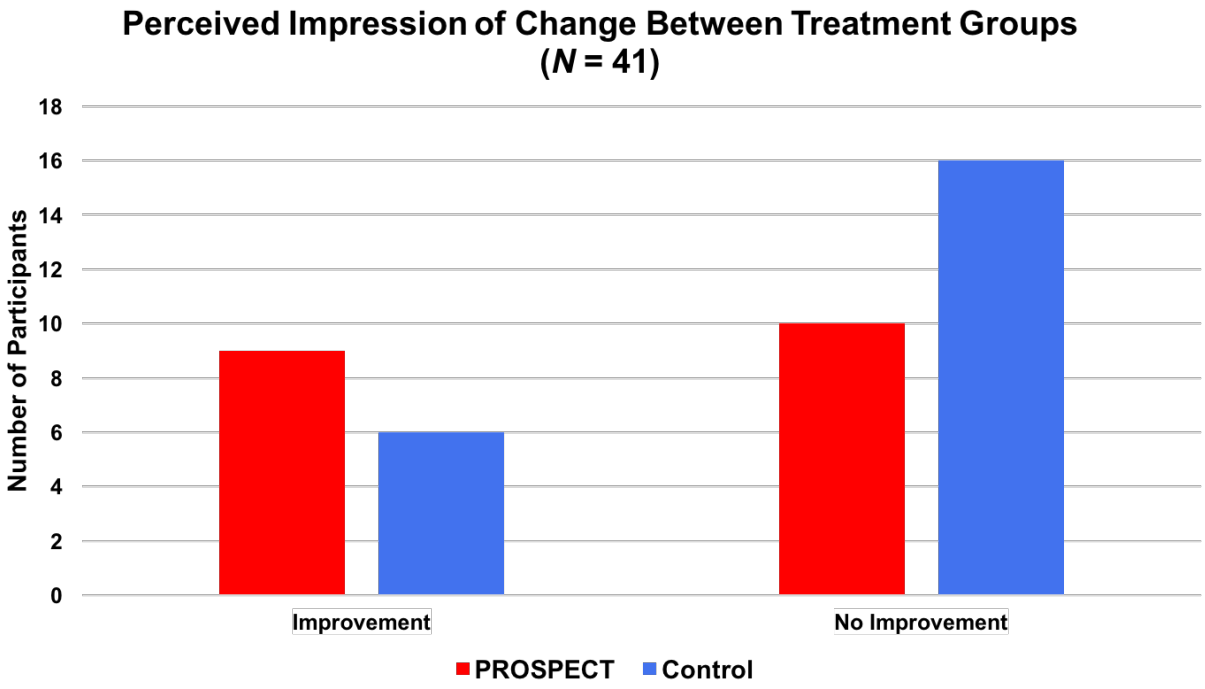
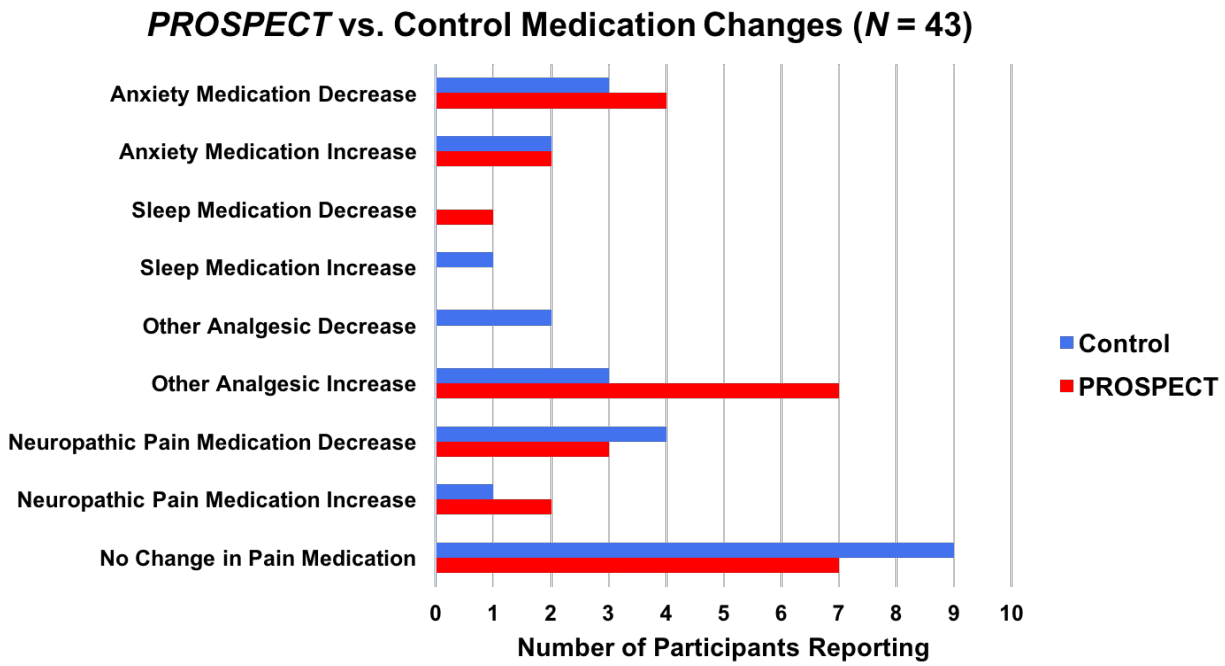


Figure 12

PROSPECT vs. Control Medication Changes During Study



Note: Medication increase/decrease refers to changes in medication dosage and/or frequency Based upon treatment recommendations for CIPN by Hershman et al. (2010), neuropathic pain medications included: duloxetine, gabapentin, pregabalin, and antidepressants. Other analgesics included: oxycodone, morphine, ibuprofen, acetaminophen

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CHAPTER V

MEDIATORS OF CHRONIC PAINFUL CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY IMPROVEMENT FOLLOWING AN EIGHT-WEEK SELF-GUIDED COGNITIVE AND BEHAVIORALLY-BASED PAIN MANAGEMENT INTERVENTION

Abstract

Context: Preliminary evidence suggests that a self-guided online cognitive and behaviorally-based pain management intervention is effective for chronic painful chemotherapy-induced peripheral neuropathy (CIPN), but, it's mechanism of action is unknown. Previous self-guided cognitive behavioral interventions have been shown to improve chronic pain-related symptoms (e.g., anxiety or depression), thus, this current intervention may target painful CIPN by addressing other symptoms.

Objectives: The purpose of this randomized controlled trial was to determine if changes in anxiety, depression, sleep-related impairment, or fatigue mediated improvements in worst pain intensity following a self-guided online cognitive and behaviorally-based pain management intervention in individuals with chronic painful CIPN.

Methods: Sixty individuals with chronic painful CIPN were randomized to receive eight weeks of self-guided cognitive behavioral pain management or treatment as usual. A seven-day worst CIPN pain intensity diary and the Patient Reported Outcome Measurement Information System (PROMIS) measures of anxiety, depression, fatigue, and sleep-related impairment were

administered at the baseline and week eight time points. Causal mediation analysis was used to quantify mediators of worst pain intensity improvement.

Results: Improvements in anxiety (β = -0.10, *CI* = -0.55, 0.37) explained the greatest proportion of the treatment effect on worst CIPN pain intensity, however, none of the hypothesized mediators had a statistically significant effect on the primary outcome (n = 37).

Conclusion: Improvements in emotional factors may mediate worst CIPN pain intensity improvements, but due to the small sample size and lack of significant findings in this current study, the evidence is still unclear. Further research is needed to identify potential mediators of pain intensity (e.g., CIPN pain-related symptoms) that can be targeted by specific cognitive behavioral strategies to improve chronic painful CIPN severity.

Background

Chronic painful chemotherapy-induced peripheral neuropathy (CIPN) occurs in 40% of individuals receiving neurotoxic chemotherapy agents such as platinums or taxanes (Kautio et al., 2011; Kolb et al., 2016; Loprinzi et al., 2011; Smith et al., 2010). Chronic painful CIPN is characterized by burning/shooting pain, numbness, and tingling in the hands and feet that can persist months to years following the completion of neurotoxic chemotherapy (Saif & Reardon, 2005; Lavoie Smith et al., 2014). Due to these symptoms, patients often report decreases in quality of life and physical functioning and may be required to terminate effective chemotherapy (Beijers, Mols, Dercksen, Driessen, & Vreugdenhil, 2014; Stubblefield et al., 2009).

Currently, there is only one treatment (duloxetine 60 mg/day) recommended for the management of chronic painful CIPN (Hershman et al., 2014; Smith et al., 2013). A randomized, waitlist-controlled trial described in Chapter IV of this dissertation examined the efficacy of a self-guided online cognitive and behaviorally-based pain management intervention called

Proactive Self-Management Program for Effects of Cancer Treatment (*PROPSECT*) on worst CIPN pain severity (Aim 1), average CIPN severity, pain interference, global impression of change, and non-painful symptoms in individuals with chronic painful CIPN (Aim 2). We found that *PROSPECT* usage significantly reduced worst pain intensity in comparison to individuals receiving treatment as usual ($p = 0.04$; $d = 0.54$). However, only 47% of individuals receiving *PROSPECT* experienced at least a 10% reduction in pain. *PROSPECT* did not work for all participants and little is known about how cognitive behavioral pain management works to improve painful CIPN, thus, further research is needed to identify mediators of pain intensity that can be targeted by *PROSEPCT* to improve the intervention's effect on painful CIPN severity.

Numerous studies provide evidence supporting the relationships between several mediating variables and cancer treatment-related pain intensity (Andersen & Kehlet, 2011; Bruce et al., 2014; Miaskowski et al., 2014; Schou Bredal, Smeby, Ottesen, Warncke, & Schlichting, 2014; Stafford et al., 2016). In addition, demographic and cancer treatment-related factors such as younger age, African American ethnicity, female gender, and oxaliplatin chemotherapy treatment are associated with increased pain severity in individuals with cancer treatment-related neuropathic pain (Dieleman, Kerklaan, Huygen, Bouma, & Sturkenboom, 2008; Hershman et al., 2016; Lewis et al., 2015; Miaskowski et al., 2014; Rustøen et al., 2004; Stafford et al., 2016; Wilson et al., 2013). Specific to chronic painful CIPN, anxiety, depression, fatigue, and sleep-related impairment have also been demonstrated to mediate pain severity (Beijers et al., 2014; Eckhoff, Knoop, Jensen, Ejlertsen, & Ewertz, 2013; Hershman et al., 2016; Smith et al., 2015; Tofthagen, 2010). For example, low emotional functioning, (i.e., anxiety and depression), fatigue, and sleep-related impairment have been shown to occur in 39%, 37%, and 24% of individuals with chronic painful CIPN (Smith et al., 2015). The relationship of these mediating

variables and chronic painful CIPN severity can be explained by the Theory of Unpleasant Symptoms (TOUS) (Chapter 1, Figure 2) (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The TOUS provides a framework for testing *PROSPECT* to address these modifiable variables that influence pain severity and how they may mediate or moderate *PROSPECT*-induced pain intensity improvements and subsequently improve overall performance (physical function).

Shared underlying pathophysiological mechanisms among anxiety, depression, fatigue, sleep- related impairment, and pain supports the hypothesis that improvements in one of these symptoms may mediate changes in worst CIPN pain intensity following cognitive behavioral pain management. These shared mechanisms include 1) structural changes in brain structures (e.g., decreased gray matter volume in the prefrontal cortex), 2) disruption of the HPA axis (e.g., increased cortisol release) and pro-inflammatory cytokine release, and 3) dysregulation of serotonergic and noradrenergic pathways. First, alterations in the prefrontal cortex (e.g., increased activation and decreased gray matter volume) have been demonstrated in individuals with anxiety/depression (heightened emotional reactivity) (Boakye et al., 2016; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011), fatigue (increased apathy, decreased goal-directed behavior) (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010; de Lange et al., 2008), sleep-related impairment (increased metabolism during sleep, leading to shallower sleep) (Boakye et al., 2016; Chao, Mohlenhoff, Weiner, & Neylan, 2014), and painful CIPN (changes in the activation of pain-processing areas in the brain such as the anterior cingulate cortex) (Nudelman et al., 2016). Alterations in the activation and structure of the prefrontal cortex may influence descending inhibitory pathways through the release of neurotransmitters which facilitate nociceptive input from the spinal cord dorsal horn to the brain (Denk, McMahon, & Tracey, 2014; Ossipov, Morimura, & Porreca, 2014). Second, disruption of the hypothalamic-pituitary-

adrenal (HPA) axis (e.g., altered cortisol functioning resulting in unchecked peripheral inflammation) and pro-inflammatory cytokine release have also been implicated in the development of chronic pain (peripheral nociceptor sensitization leading to continual nociceptive signaling to spinal cord dorsal horn) (Johnson & Greenwood-Van Meerveld, 2014), depression/anxiety (HPA sensitization due to stress) (Boakye et al., 2016; Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008), fatigue (increased cortisol response may influence circadian rhythms (Barsevick et al., 2010; Thornton, Andersen, & Blakely, 2010), and sleep-related impairment (wakefulness associated with cortisol release) (Boakye et al., 2016; Thornton, Andersen, & Blakely, 2010). Third, the neurotransmitters (i.e., serotonin and norepinephrine) that are involved in descending pain modulation are also involved in the development of fatigue (increased levels of serotonin or upregulation of serotonin receptors alters HPA axis to reduce somatic drive) (Barsevick et al., 2010), sleep-related impairment (decreased availability of serotonin associated with insomnia) (Smith et al., 2009), depression (decreased availability of serotonin) (Boakye et al., 2016), and anxiety (activation of amygdala and anterior cingulate cortex influencing descending pain modulation) (Zhuo, 2016). Overall, due to the overlapping pathophysiological mechanisms of pain and co-occurring symptoms, targeting interventions that work to address one of the pathophysiological mechanisms shared by these co-occurring symptoms may result in pain intensity improvement.

Cognitive behavioral pain management may work to decrease pain intensity by inducing structural changes in the brain, which subsequently may influence descending inhibitory nociceptive pathways through the release of norepinephrine and serotonin. For example, recent evidence suggests that cognitive behavioral pain management increases gray matter volume in the prefrontal cortex, which may increase access to executive control function and allow

individuals to reappraise and subsequently gain control over their experience of pain. These cognitive behavioral pain management-induced structural changes in the prefrontal cortex may lead to the release of neurotransmitters which "gate" or block nociceptive transmission from the spinal cord to the brain (Jensen et al., 2012; Seminowicz et al., 2013). Cognitive behavioral pain management may also improve stress, thereby correcting HPA axis dysfunction. Thus, because chronic painful CIPN co-occurs with symptoms that share similar pathophysiological mechanisms and cognitive behavioral pain management targets mechanisms that are common to all symptoms, it's possible that improvements in anxiety, depression, fatigue, or sleep-related impairment may also improve pain. For example, previous studies have shown that improvements in stress, anxiety, depression, catastrophizing, and perceived control over pain have mediated improvements in chronic pain intensity in other neuropathic pain populations (i.e., temporomandibular, low-back, and arthritis pain) (DasMahapatra, Chiauzzi, Pujol, Los, & Trudeau, 2015; McCracken, Gross, & Eccleston, 2002; Turner, Holtzman, & Mancl, 2007). However, we are unaware of published studies that have examined mediators of pain intensity improvement following self-guided cognitive behavioral pain management in individuals with chronic painful CIPN. The identification of specific mediators of painful CIPN may allow for further investigation regarding which cognitive behavioral strategies may be most effective in targeting the identified mediators and subsequently, reducing CIPN pain intensity.

Purpose

In Chapter IV, we presented our findings related to Aims 1 and 2 of this randomized controlled trial, which were to test the efficacy of an eight week self-guided online cognitive and behaviorally-based pain management intervention (*PROSPECT*) to improve worst CIPN pain intensity (Aim 1), average CIPN pain intensity, pain interference, non-painful CIPN symptom

severity (e.g., numbness and tingling), and global impression of change (Aim 2) in individuals with chronic painful CIPN in comparison to individuals receiving treatment as usual. The focus of Chapter V is to report the findings relevant to Aim 3a; to examine the mediating effect of mean changes in sleep-related impairment, anxiety, depression, or fatigue on worst pain intensity following eight weeks of *PROSPECT* in individuals with chronic painful CIPN. Secondarily, we also assessed the efficacy of the *PROSPECT* intervention to reduce anxiety, depression, fatigue, and sleep-related impairment (Aim 3b). Lastly, we conducted an exploratory analysis to determine whether baseline pain-related symptom severity and demographic/cancer-related variables moderate worst pain intensity improvement following *PROSPECT* (Aim 3c).

Methods

Setting and Sample

Sixty patients were recruited from five academic and/or community outpatient cancer centers from May 1, 2016 to October 4, 2016. Eligible patients were adults with self-reported 4/10 or greater worst CIPN pain intensity for three months following the completion of neurotoxic chemotherapy, had at least National Cancer Institute Common Terminology Criteria for Adverse Events grade one sensory peripheral neuropathy (National Cancer Institute, 2010), had a stable analgesic medication regimen (≤ 10% change in dosage in the two weeks prior to study enrollment), and self-reported the ability to use a computer. Patients were excluded if they had neuropathy due to other causes or planned to receive neurotoxic chemotherapy at any point during the study. This study was approved by the Institutional Review Board associated with each study site and written informed consent was obtained from all participants.

Measures

An 11 – point numerical rating scale ("10" represents worse pain) was used to measure worst CIPN pain severity (Cleeland & Ryan, 1994; Dworkin et al., 2005), and was administered via a seven – day diary at the baseline and eight week time points. An 11 – point numerical rating scale is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials and several studies support the scale's reliability and validity (Dworkin et al., 2005; Hjermstad et al., 2008; Jensen, Karoly, & Braver, 1986; Li, Liu, & Herr, 2007).

The Patient Reported Outcome Measurement Information System (PROMIS) Sleep-related Impairment 8a (four items; 1, not at all; 5 very much; transformed total score range 30.0 – 80.1) measures self-reported perceptions of alertness, sleepiness, tiredness during the day, and functional impairment associated with poor sleep over the past seven days (National Institute of Health Patient-Reported Outcomes Measurement Information System, 2014). The internal consistency reliability alpha coefficient of the Sleep-Related Impairment 8a is 0.90 (Yu et al., 2012). Satisfactory convergent validity is supported by strong correlations between the PROMIS Sleep-Related Impairment 8a and the Pittsburgh Sleep Quality Index ($r = 0.65$) (Yu et al., 2012).

The PROMIS Anxiety 4a (four items; 1, never; 5, always; transformed total score range 40.3 – 81.6) measures self-reported fearfulness, worry, nervousness, and uneasiness over the past seven days (National Institute of Health Patient-Reported Outcomes Measurement Information System, 2014). The internal consistency reliability alpha coefficient is 0.89 (Kroenke, Yu, Wu, Kean, & Monahan, 2014). Satisfactory convergent validity is evidenced by strong correlations between the PROMIS Anxiety 4a and the Generalized Anxiety Disorder-7 ($r = 0.79$) and the 5-Item Mental Health Inventory in a chronic pain population ($r = 0.85$) (Kroenke et al., 2014).

The PROMIS Emotional Distress-Depression 4a (four items; 1, never; 5, always; transformed total score range 41.0 – 79.4) examines self-reported negative mood, views of self,

and decreased positive affect and engagement over the past seven days (National Institute of Health Patient-Reported Outcomes Measurement Information System, 2014). The internal consistency reliability alpha coefficient is 0.98 and the test-retest reliability is satisfactory (r = 0.86) (Bartlett et al., 2015). Satisfactory convergent validity is evidenced by strong correlations between the PROMIS Depression 4a and the Patient Health Questionnaire-9 (r = 0.75) and the 5-Item Mental Health Inventory in a chronic pain population (r = -0.85) (Kroenke et al., 2014).

The PROMIS Fatigue 4a (4 items; 1, not at all; 5 very much; transformed total score range 33.7 – 75.8) measures self-reported feelings of tiredness and exhaustion that likely decrease one's ability to perform daily activities and function normally in family/social roles (National Institute of Health Patient-Reported Outcomes Measurement Information System, 2014). There is strong evidence supporting the instrument's reliability and validity. The internal consistency reliability alpha coefficient is 0.98 (Bartlett et al., 2015). Satisfactory convergent validity is evidenced by strong correlations between the PROMIS Fatigue 4a and the Fatigue Visual Analogue Scale (r = 0.86) (Bartlett et al., 2015).

Procedures

The procedures of the randomized controlled trial have been previously described in Chapter IV, but are briefly described here. Following informed consent, participants completed the worst CIPN pain diary (day one) and the PROMIS subscales via computer tablet. The principal investigator then randomized participants to either eight weeks of *PROSPECT* or treatment as usual in a 1:1 ratio using a computer generated random numbers table. Participants then received a paper copy of the seven-day worst CIPN pain diary and submitted their scores via an emailed survey link. After completing the pain diary, participants were either emailed a password protected link to the *PROSPECT* website or instructions about the control intervention.

The *PROSPECT* website contains cognitive behavioral strategies (e.g., activity pacing, relaxation, sleep hygiene) and self-management information (e.g., patient-provider communication about symptoms, goal setting, educational information regarding common cancer treatment-related symptoms) designed to help individuals manage pain and pain-related symptoms (e.g., anxiety, depression, fatigue, sleep-related impairment) (Kerns et al., 2011; Knoerl et al., 2015; Williams, Eccleston, & Morley, 2012). Participants were encouraged to use the *PROSPECT* website as much as they desired and to use the strategies most pertinent to the symptoms they were experiencing. Eight weeks following randomization, participants were emailed electronic versions of the worst CIPN pain diary and PROMIS measures. Participants were reminded to complete the surveys via a telephone call at the eight week time point, and one week later. In terms of adherence to treatment, participants in both groups were emailed weekly surveys asking about the number of minutes spent using *PROSPECT* and/or other symptom management resources. Additionally, participants were contacted via telephone four and eight weeks after randomization to determine if they changed the dosages of any of their medications for anxiety, depression, fatigue, pain, or sleep-related impairment. Demographic and cancer treatment-related information was abstracted from the patient's electronic medical record at baseline by trained study staff.

Statistical Analyses

Aim 3a. R version 3.3.2 was utilized to analyze all data (R Development Core Team, 2017). The sample analyzed was based on individuals who completed all baseline and week eight survey data. A power analysis was conducted for the primary mediation aim using the *powerMediation.VSMc* function from the *powerMediation* package (Qiu, 2015; Vittinghoff, Sen, & McCulloch, 2009). The sample size calculation was based on an effect size of 0.64 (Williams

et al., 2010). The correlation between the predictor and the mediator was set at a range of 0.1 to 0.5. To have 80% power for the primary analysis, 25 participants were needed in the *PROSPECT* and wait-list control groups, respectively.

We used causal mediation (Imai, Keele, & Tingley, 2010) to determine if changes in anxiety, depression, fatigue, and sleep-related impairment over the eight week treatment period would mediate the effects of *PROSPECT* on worst pain intensity improvement (Figure 13). The causal mediation effect is defined as the indirect effect of the treatment on the dependent variable through the mediators (Paths "A" and "B" in Figure 13). The direct effect is the effect of the treatment on the dependent variable (Path "C" in Figure 13). The total effect represents the sum of the indirect and total effects (Imai et al., 2010). Using linear regression techniques, we modeled 1) the mediators (anxiety, depression, fatigue, and sleep-related impairment mean change scores, respectively) given the treatment and baseline covariates (i.e. baseline worst pain scores and age) and 2) the outcome (worst pain intensity mean change score) given the treatment, mediator, and baseline covariates (Imai et al., 2010; Imai, Keele, Tingley, & Yamamoto, 2015). These two models were then combined into the *mediate* function from the *Mediation* (Tingley et al., 2015) package to estimate the causal mediation effect and 95% confidence interval of the causal mediation effect for each mediation model. Lastly, sensitivity analyses were conducted using the *medsens* function from the *Mediation* (Tingley et al., 2015) package to assess for unobserved confounders to determine the validity of the analysis (Imai et al., 2010, 2015).

Aims 3b and 3c. First, to determine the efficacy of *PROSPECT* on pain-related outcomes, week eight mean scores in anxiety, depression, sleep-related impairment, and fatigue were compared between groups using ANCOVA adjusting for baseline scores and age. Second, we examined if baseline anxiety, depression, fatigue, and sleep-related impairment symptom

severity or demographic/cancer-related variables (i.e. age, gender, chemotherapy type) moderated improvements in worst CIPN pain intensity. Worst CIPN pain intensity mean change scores were calculated for the subgroups of young/old age, gender, chemotherapy type, and low/high PROMIS subscale scores. Young/old age and low/high PROMIS subscale scores were determined based on median scores for the total sample.

Results

Sample Characteristics

Demographic and cancer diagnosis/treatment-related characteristics of the recruited sample are described in Table 7 (Chapter IV). The mean age of the study participants was 61.15 (*SD* = 9.06, *Range* = 40 – 78) years old. The sample was mainly female (75%), Caucasian (91.7%), college educated (82.1%), retired (43.4%), married (70%), and regularly used a computer (85%). Individuals in the *PROSPECT* group had higher levels of fatigue and sleep-related impairment in comparison to individuals in the control group, otherwise, there were no differences between groups. When comparing protocol completers vs. non-completers, more non-completers had stage IV cancer (46% in comparison to 19% for completers), but, baseline pain and pain-related symptom severity did not differ between the two groups. Of the 60 participants recruited in the study, 37 participants provided complete baseline and week eight data (*PROSPECT N* = 18, Control *N* = 19) for Aim 3a, 42 (*PROSPECT N* = 19, Control *N* = 23) for Aim 3b, and 38 for Aim 3c (*PROSPECT N* = 19, Control *N* = 19).

Aim 3a

Table 11 shows the results of the test of the indirect effect of *PROSPECT* on worst pain intensity through each proposed mediator. Mean changes in anxiety (β = -0.10) explained the greatest percentage of the total effect of *PROSPECT* treatment on worst pain intensity, however

none of the proposed mediators significantly mediated the effect of *PROSPECT* on worst pain intensity. Results of sensitivity analyses revealed that none of the mediation models violated the sequential ignorability assumption (Imai et al., 2015).

Aim 3b

Individuals receiving *PROSPECT* had greater improvements in anxiety, fatigue, and sleep-related impairment than individuals receiving usual care, but, the differences in improvement were not statistically significant (Table 12). Trends in anxiety, depression, and fatigue (Figures 14 - 16) across time also indicated that *PROSPECT* provided no clear benefit over usual care. Trends in sleep-related impairment severity suggested that individuals receiving *PROSPECT* were experiencing consistent improvements as the study progressed (Figure 17).

Aim 3c

Table 13 and/or Figures 18 – 24 describe worst CIPN pain intensity mean change scores based on baseline young/old age, chemotherapy type, gender, and low/high symptom severity. Individuals in the *PROSPECT* treatment arm, regardless of subgroup (e.g., low/high symptom severity), had greater improvements in worst CIPN pain intensity than individuals receiving usual care. Specifically, individuals receiving *PROSPECT* who were categorized in the low baseline severity group for pain, depression, anxiety, sleep-related impairment, and fatigue experienced greater improvements in worst pain intensity than individuals who were classified in the high severity group. As for demographic characteristics, older adults (≥ 61) (n = 7; *mean* = -1.47, *SD* = 1.54) receiving *PROSPECT* had greater improvements in worst CIPN pain intensity than did younger adults (< 61) (n = 12; *mean* = -0.63, *SD* = 1.21). Males (n = 3; *mean* = -1.14, *SD* = 1.27) and females (n = 16; *mean* = -0.96, *SD* = 1.42) receiving *PROSPECT* experienced similar decreases in worst pain intensity. Finally, individuals receiving *PROSPECT* with taxane-

related CIPN (n = 9; *mean* = -1.16, *SD* = 1.60) experienced greater improvements in worst CIPN pain intensity than individuals with platinum-related CIPN (n = 8; *mean* = -0.44, *SD* = 0.91).

Discussion

The results of the analysis addressing Aim 3a revealed that none of the hypothesized influencing factors of chronic painful CIPN significantly mediated worst CIPN pain intensity improvement following eight weeks of *PROSPECT*. *PROSPECT* was also not shown to significantly improve anxiety, depression, fatigue, or sleep-related impairment severity in comparison to individuals receiving treatment as usual (Aim 3b). Finally, individuals who were older or experienced low baseline CIPN pain-related symptom severity reported the greatest improvements in worst CIPN pain intensity following *PROSPECT* usage (Aim 3c). The negative findings of this study may be explained by study design features that negatively influenced the internal validity of the study. First, the study was underpowered, which may increase the probability of finding a false negative result (Type II error). Second, participants only interacted with the *PROSPECT* website for eight weeks. Therefore, participants may not have had enough time to learn and incorporate the strategies from the website into their day-to-day life to influence behavior change related to pain management. While these threats to internal validity may be primarily responsible for the lack of statistically significant findings in this chapter, additional explanations for the negative findings are presented.

The objective of Aim 3a was to examine the mediating effect of changes in anxiety, depression, fatigue, and sleep-related impairment on worst CIPN pain intensity. Results demonstrated that improvements in anxiety mediated the greatest proportion of the effect of *PROSPECT* on worst CIPN pain intensity. These results are aligned with previous studies that have demonstrated that emotional factors mediate pain intensity improvement following in-

person (i.e., anxiety) and online (i.e., stress and depression) cognitive behavioral pain management (DasMahapatra et al., 2015; McCracken et al., 2002). Although none of the hypothesized mediating variables significantly mediated the effect of *PROSPECT* on worst CIPN pain intensity, due to the small sample size (increased probability of Type II Error), these variables should be examined in future research. Alternatively, because anxiety, depression, fatigue, and sleep-related impairment share common underlying pathophysiological mechanisms (Barsevick et al., 2010; Boakye et al., 2016; Zhuo, 2016), improvements in pain intensity may be mediated through improvements in multiple symptoms. Therefore, we may have missed this synergistic mediating effect due to our usage of a single mediation model.

While we assessed the mediating effect of anxiety, depression, fatigue, and sleep-related impairment on worst CIPN pain intensity, based on the TOUS, there are other influencing factors that may mediate worst CIPN pain intensity improvement that we did not measure. Specifically, cognitive variables (e.g., perceived control over pain, pain catastrophizing, and self-efficacy to manage pain) have been shown to mediate chronic pain improvement in prior research. For example, a study by Turner, Holtzman, & Mancl (2007) demonstrated that improvements in perceived control over pain, self-efficacy to manage pain, harm beliefs (belief that pain indicates damage and activity should be avoided), disability beliefs (belief that one's pain is disabling), and pain catastrophizing (belief that pain is superlatively awful in its experience and its impact) mediated reductions in chronic temporomandibular disorder pain intensity following in-person cognitive behavioral pain management (Turner et al., 2007). Specifically, increased perceived control over pain explained the greatest percentage (81%) of the total effect of treatment on pain improvement. An additional study also found that pain catastrophizing mediated improvements in pain intensity following in-person cognitive behavioral therapy in individuals with chronic

low back pain (Smeets, Vlaeyen, Kester, & Knottnerus, 2006). Further, increases in gray matter volume in the prefrontal cortex (region associated with executive control), hippocampus, and anterior cingulate have been shown to be associated with decreases in pain catastrophizing following cognitive behavioral pain management (Seminowicz et al., 2013). Overall, there is considerable evidence supporting the mediating role of cognitive variables in pain intensity improvement following cognitive behavioral pain management. *PROSPECT* may be modified to incorporate strategies such as cognitive restructuring (e.g., identifying and reframing automatic negative thoughts about symptoms such as pain, anxiety, depression) (Kerns et al., 2011) to target cognitive variables such as catastrophizing in subsequent studies.

The objective of Aim 3b was to evaluate the efficacy of *PROSPECT* on key CIPN pain-related symptoms. While individuals receiving *PROSPECT* did appear to experience modest improvements in sleep-related impairment in comparison to individuals receiving usual care, results demonstrated that there were no significant differences in anxiety, depression, fatigue, or sleep-related impairment mean change scores between groups. One possible reason for the lack of significant improvement in co-occurring symptoms is that the *PROSPECT* intervention did not contain enough strategies to adequately address these symptoms. For example, cognitive restructuring, a key strategy of cognitive behavioral therapy for anxiety and depression, was not included in *PROSPECT* (Beck, Beck, & S., 2010). Cognitive restructuring (Kerns et al., 2011) has been demonstrated to be a key component of previous self-guided cognitive behavioral pain management interventions. Of the seven-self-guided cognitive behavioral pain management trials reviewed by Knoerl et al. (2015), four (Buhrman et al., 2013; Carpenter, Stoner, Mundt, & Stoelb, 2012; Dear et al., 2013; Ruehlman, Karoly, & Enders, 2012) had positive effects on anxiety/depression. These four trials placed a specific emphasis on cognitive restructuring by

providing increased exposure to the cognitive restructuring specific module (e.g., multiple weeks). Conversely, programs that focused more on self-management (e.g., communication with provider, medication management, goal setting) and contained less content related to cognitive restructuring were less effective for anxiety/depression. Future prototypes of *PROSPECT* should include and emphasize modules specific to cognitive restructuring strategies to target symptoms such as anxiety and depression.

Less is known regarding the efficacy of cognitive behavioral pain management for pain-related fatigue and sleep-related impairment in individuals with chronic pain. Only one self-guided cognitive behavioral pain management trial (Williams et al., 2010) included in the Knoerl et al. (2015) integrative review examined fatigue or sleep-related outcomes in individuals with chronic pain (no positive findings). However, there is considerable evidence supporting the use of cognitive behavioral therapy for insomnia and fatigue (Price, Mitchell, Tidy, & Hunot, 2008; Zachariae, Lyby, Ritterband, & O'Toole, 2016). For instance a recent randomized controlled trial by Ritterband et al. (2017) tested a self-guided cognitive behavioral intervention for sleep that incorporated sleep hygiene, sleep restriction, stimulus control, relapse prevention, and cognitive restructuring strategies. Results suggested that individuals receiving the intervention had significantly improved insomnia severity ($p < 0.001$) in comparison to individuals receiving insomnia education (Ritterband et al., 2017). Moreover, strategies aimed at managing and increasing physical activity have been shown to be effective for fatigue (Cramp & Byron-Daniel, 2012; Larun, Brurberg, Odgaard-Jensen, & Price, 2016). Thus, future prototypes of *PROSPECT* may explore adding strategies related to sleep restriction (e.g., sleeping/waking at certain times to relearn proper sleep dynamics), cognitive restructuring strategies in the context of sleep-

related impairment, and additional ways to manage and increase physical activity to target fatigue and sleep-related impairment in individuals with chronic painful CIPN.

The objective of Aim 3c was to examine the effect of baseline demographic and cancer treatment-related variables on changes in worst CIPN pain intensity. Overall, previous studies examining pain intensity improvement following cognitive behavioral pain management have not revealed any specific moderator variables, suggesting that this intervention may be beneficial for a variety of individuals (DasMahapatra et al., 2015; Turner et al., 2007; Underwood, Mistry, Lall, & Lamb, 2011). We found similar findings in regard to gender, as males and females receiving *PROSPECT* experienced similar improvements in worst CIPN pain intensity. However, modest improvements in worst CIPN pain intensity were observed in several demographic and cancer-specific subgroups. The results of this aim are exploratory in nature because this was not a planned aim of the study and we were underpowered.

Older adults (age > 61) reported greater improvements in worst CIPN pain intensity than younger adults following use of *PROSPECT*. This finding is not surprising as several studies provide evidence for the efficacy of cognitive behavioral pain management for older adults (Berman, Iris, Bode, & Drengenberg, 2009; Broderick et al., 2014; Keefe, Porter, Somers, Shelby, & Wren, 2013; Wetherell et al., 2016). Further, a secondary analysis by Wetherell et al. (2016) found that older adults with chronic pain receiving an acceptance and commitment-based treatment experienced greater improvements in pain intensity than younger adults, but, younger adults had a greater treatment response to a cognitive behavioral pain management intervention. The differences in pain response following cognitive behavioral interventions between younger and older adults may be related to past experiences with pain treatment. Older adults may have experienced more “failed” attempts with pain management interventions (e.g., medications) and

subsequently, may be more receptive to interventions focused on accepting and self-managing pain (non-curative focus). On the other hand, younger adults may want to continue to pursue potentially curative interventions for chronic pain and may not be as receptive to interventions focusing on acceptance (Wetherell et al., 2016). Lastly, additional studies are needed to examine the efficacy of self-guided cognitive behavioral pain management interventions for older adults with chronic pain because this population is less likely to able to use a computer (File, 2013).

Several baseline pain-related symptoms were shown to moderate improvements in worst CIPN pain intensity. Individuals with low baseline depression/anxiety scores receiving *PROSPECT* were more likely to experience improvements in worst CIPN pain intensity than individuals with high baseline depression/anxiety. These findings are consistent with a prior study that examined moderators of pain intensity improvement in individuals with chronic painful CIPN. Smith et al. (2015) identified that individuals with high baseline emotional functioning receiving duloxetine were more likely to have a clinically significant improvement in pain intensity than those with low baseline emotional functioning (Smith et al., 2015). Higher rates of depression have also been associated with poorer response (< 30% pain reduction) to self-guided cognitive behavioral pain management three months post treatment (Dear et al., 2016). Similarly, individuals receiving *PROSPECT* who were classified in the low fatigue or sleep-related impairment subgroups had greater improvements in worst CIPN pain than individuals in the high severity subgroups.

Overall, these findings may be attributed to shared underlying mechanisms among CIPN pain and pain-related symptoms. For example, chronic pain, depression, and sleep- related impairment share several underlying pathophysiological mechanisms 1) activation and structural changes in similar brain structures (e.g., prefrontal cortex and limbic system), 2) dysregulation of

the HPA axis (e.g., increased cortisol release), 3) alterations in serotonergic and noradrenergic pathways, and 4) increased pro-inflammatory cytokine release (Boakye et al., 2016). Thus, individuals with low CIPN pain-related symptom severity may require less intervention (e.g., lower cognitive behavioral pain management dose) to experience a reduction in pain because they have compensatory mechanisms (e.g., sufficient emotional functioning) that share the same physiologically pathways as pain. Conversely, individuals with higher CIPN pain-related symptom severity may need additional interventions (e.g., medications) or greater cognitive behavioral pain management dose to experience a reduction in pain because they have multiple co-occurring conditions disrupting regulatory processes within the central nervous system.

There are several limitations to this study. First, due to attrition and small sample size, we were underpowered for our primary mediation analysis and secondary analyses. Study results demonstrated that no single co-occurring symptom mediated the effects of treatment on worst CIPN pain intensity, but, because we were underpowered, these variables should be retested in a larger study to examine the true mediating effect of these co-occurring symptoms on CIPN pain intensity. Similarly, due to small sample size and lack of formal statistical testing, potential moderators of worst CIPN pain intensity improvement should be further evaluated in larger studies. Second, we only examined symptom severity over eight weeks. It is possible that we may have observed greater improvements in worst pain and pain-related symptoms if individuals had more time to interact with the strategies of *PROSPECT* because behavior change takes time. Third, due to low *PROSPECT* usage by individuals in the intervention group (results presented in Chapter IV) and the self-guided nature of the intervention, perhaps participants did not receive the optimal dose of the intervention to decrease pain-related symptoms. Fourth, the participants had a high degree of computer literacy, therefore, the results are not generalizable to individuals

with low computer literacy or individuals who do not have computer access. Fifth, differences in response to *PROSPECT* may have been attributed to differences in chemotherapy drug-specific (e.g., platinums/taxanes) mechanisms of peripheral nerve injury. While peripheral pathophysiological mechanisms vary by CIPN (Carozzi et al., 2015), we did not control for CIPN type in our analysis because there is no evidence suggesting that cognitive behavioral pain management improves non-painful CIPN symptoms CIPN pain or pain-related symptoms through peripheral mechanisms. Sixth, higher pain medication and other symptom management activity use by individuals in *PROSEPCT* (Table 10 and Figure 12; Chapter IV) may have confounded our results related to differences in improvement in anxiety, depression, fatigue, or sleep-related impairment between groups. Lastly, individuals receiving *PROSPECT* may not have experienced greater decreases in pain-related symptom severity than individuals receiving usual care because individuals receiving *PROSPECT* had greater pain-related symptom severity at baseline. To control for these differences, we included baseline severity as a covariate in our analyses aimed at determining differences in pain-related symptom improvement between groups. Despite these limitations, the results of this study contribute to the growing body of literature surrounding the identification of moderators and mediators of pain intensity improvement following cognitive behavioral pain management to gain a greater understanding of how this treatment may work to improve pain intensity and who it works for.

In conclusion, anxiety mediated the greatest proportion of the effect of *PROSPECT* on worst CIPN pain intensity, however, none of the hypothesized mediators of chronic painful CIPN were significant. Due to the small sample size, the mediating effect of these co-occurring symptoms of CIPN should be reevaluated in a larger study. Additional next steps include examining the mediating effect of other variables known to influence pain severity (e.g., self-

efficacy to manage pain, stress, or perceived control over pain) or the summative effect of several different mediating variables on pain intensity (e.g., anxiety and depression) in a larger sample. Moreover, *PROSPECT* did not significantly improve anxiety, depression, fatigue, or sleep-related impairment severity in comparison to control in individuals with chronic painful CIPN, but, there did appear to be trends in sleep-related impairment improvement. Further research is needed to revise the *PROSPECT* modules focused on these symptoms and to test the effect of *PROSPECT* in a larger sample to evaluate the true effect of the intervention on these outcomes. Lastly, exploratory analyses revealed several baseline variables (e.g., older age, taxane-chemotherapy receipt, low depression) that led to considerable improvements in worst pain intensity in individuals receiving a self-guided online cognitive and behaviorally-based pain management intervention. The moderating effect of these variables on improvements in worst CIPN pain intensity should be tested in a larger study using formal statistical testing. The identification of moderators and mediators of pain intensity in individuals with painful CIPN will allow for the targeting of behavioral strategies to factors known to improve pain intensity.

Table 11

Mediators of PROSPECT Effects on Worst Pain Intensity Mean Change Scores

Treatment Effect (*N* = 37)	**Estimate (95% *CI*)**	**Total Effect Explained by Mediators (%)[c]**
Total Treatment Effect[a]	-1.14 (-2.08, - 0.20)	
Indirect Effect		
Depression	-0.01 (-0.21, 0.25)	0
Anxiety	-0.10 (-0.55, 0.37)	9.0
Sleep-related Impairment	-0.08 (-0.42, 0.11)	7.0
Fatigue	-0.07 (-0.45, 0.12)	6.1

Note: [a] Unstandardized regression coefficient (95% CI) for treatment effects (*PROSPECT* vs. control) on worst pain intensity mean change scores (change scores were calculated by subtracting baseline from week eight subscale scores only in patients who provided baseline and week eight scores), unadjusted for mediators but adjusted for baseline worst pain intensity scores and age.

[b] Test of the statistical significance of the indirect effect of treatment (*PROSPECT* vs. control) on week eight worst pain intensity mean change scores through the mediators.

[c] Calculated by dividing the indirect effect by the total treatment effect (top row).

Table 12

Mean Scores for PROMIS Subscale Scores from Baseline to Week Eight

Outcomes (*N* = 42)	**Intervention Mean (*SD*)**	**Control Mean (*SD*)**	**Intervention Mean Change (*SD*)[a]**	**Control Mean Change (*SD*)[a]**
Sleep-related Impairment				
Baseline	58.93 (6.44)	55.61 (5.77)	-2.42 (4.05)	-1.29 (3.39)
Week Eight	56.41 (5.96)	54.32 (5.79)		
Fatigue				
Baseline	59.18 (6.82)	53.14 (7.69)	-2.53 (5.99)	-1.69 (5.26)
Week Eight	56.74 (8.42)	51.45 (7.67)		
Depression				
Baseline	52.02 (7.49)	48.11 (7.33)	-0.46 (6.15)	-1.27 (5.02)
Week Eight	51.56 (7.35)	46.84 (6.21)		
Anxiety				
Baseline	53.63 (7.94)	50.32 (7.82)	-1.26 (5.42)	-1.05 (8.46)
Week Eight	52.37 (8.65)	49.27 (7.15)		

[a] Change scores were calculated by subtracting baseline from week eight subscale scores only in patients who provided baseline and week eight scores.

Table 13

Worst Pain Intensity Mean Change Scores Based on Baseline Characteristics

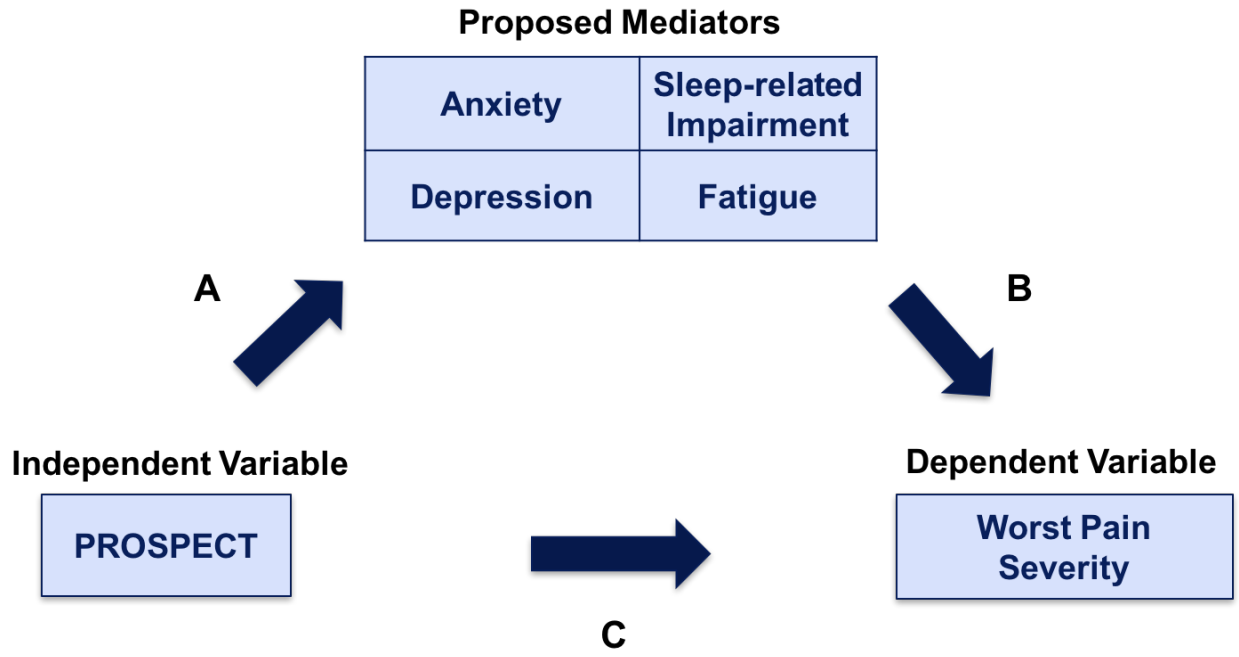
Variable (*N* = 38)	**Median[a]**	***PROSPECT***			**Control**		
		Mean	***SD***	***n***	**Mean**	***SD***	***n***
Age	61						
Young		-0.63	1.21	12	0.05	0.80	6
Old		-1.47	1.54	7	-0.02	1.52	13
Gender							
Male		-1.14	1.27	3	-0.22	1.68	6
Female		-0.96	1.42	16	0.10	1.28	13
Chemotherapy							
Platinums		-0.44	0.91	8	-0.53	0.82	9
Taxanes		-1.16	1.60	9	-0.14	1.33	7
Other*		-1.93	1.72	2	1.67	1.09	3
Pain	4.57						
Low		-0.84	1.39	7	0.50	1.23	10
High		-1.0	1.41	12	-0.56	1.23	9
Depression	51.80						
Low		-1.52	1.44	6	0.41	1.02	12
High		-0.69	1.30	13	-0.69	1.54	7
Anxiety	53.70						
Low		-1.25	1.37	8	0.44	1.14	10
High		-0.71	1.38	11	-0.49	1.38	9
Fatigue	57.0						
Low		-1.32	1.51	4	-0.06	1.46	14
High		-0.83	1.36	15	0.17	0.90	5
Sleep-related Impairment	57.20						
Low		-1.0	1.65	5	0.13	1.59	11
High		-0.92	1.32	14	-0.18	0.87	8

Note: Young/old age and low/high symptom scores based on median of the total sample for each respective variable.

*Other chemotherapy types included bortezomib and vinca alkaloids

Figure 13

Proposed Mediation Model of PROSPECT on Worst CIPN Pain Intensity



Note: Paths "A" and "B" represent the indirect effect of *PROSPECT* on worst CIPN pain intensity as explained through the mediators
Path "C" represents the direct effect of *PROSPECT* on worst CIPN pain intensity.

Figure 14

Effect of Treatment Group on Anxiety

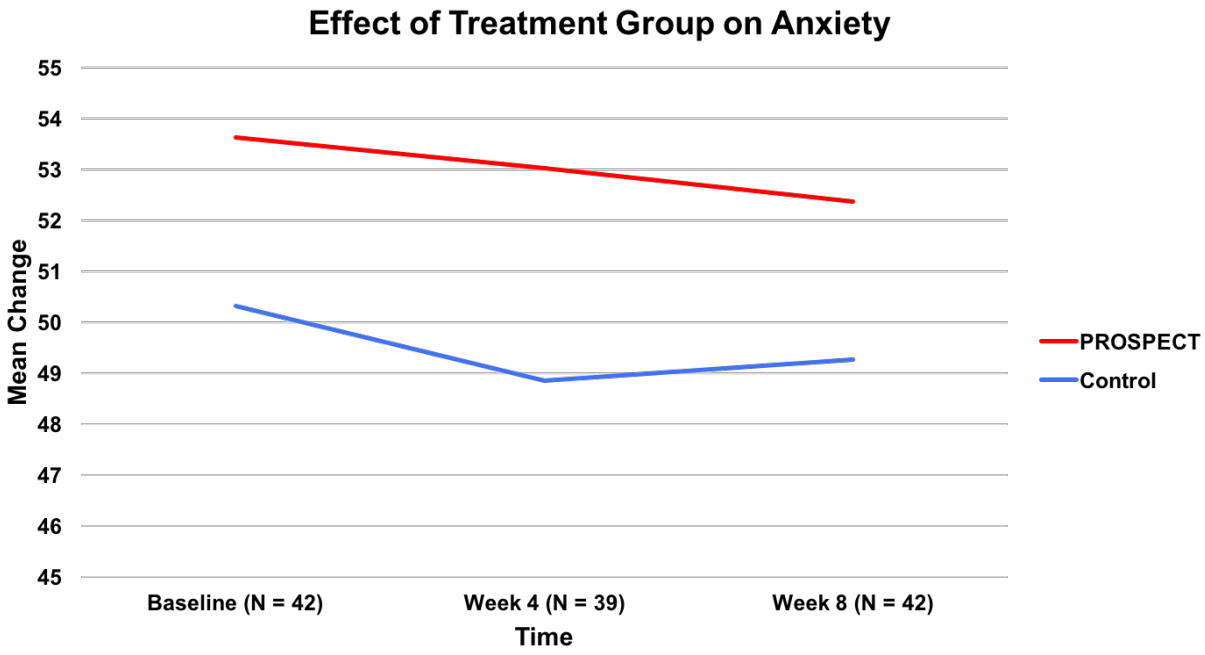


Figure 15

Effect of Treatment Group on Fatigue

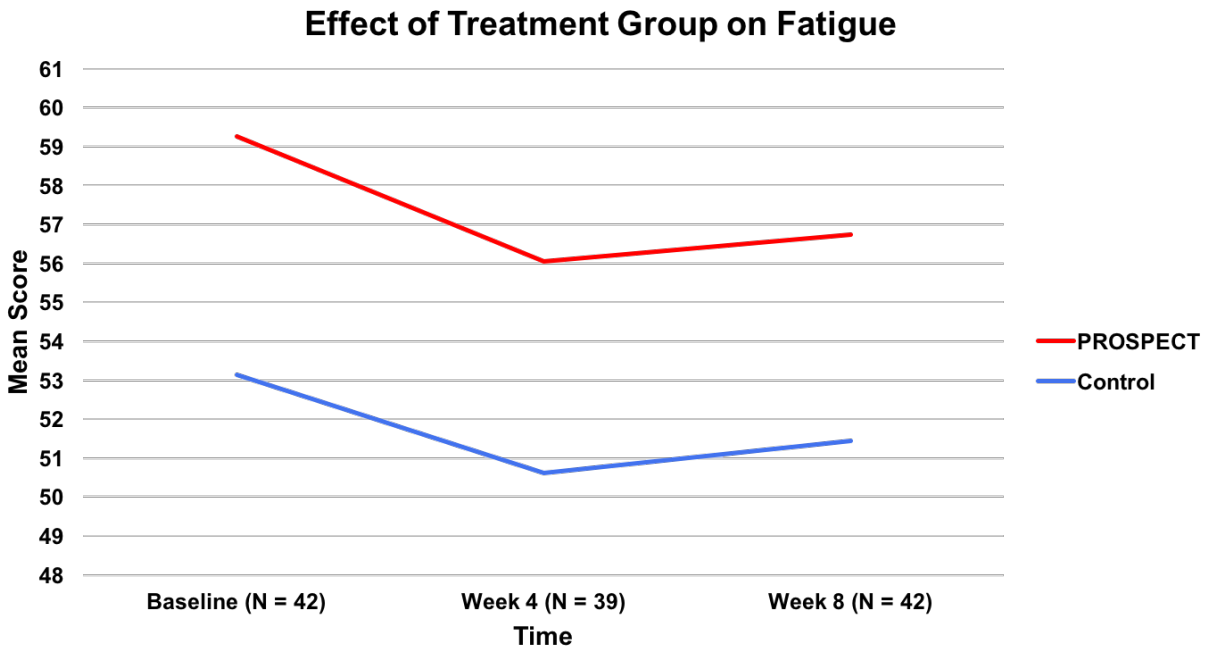


Figure 16

Effect of Treatment on Depression

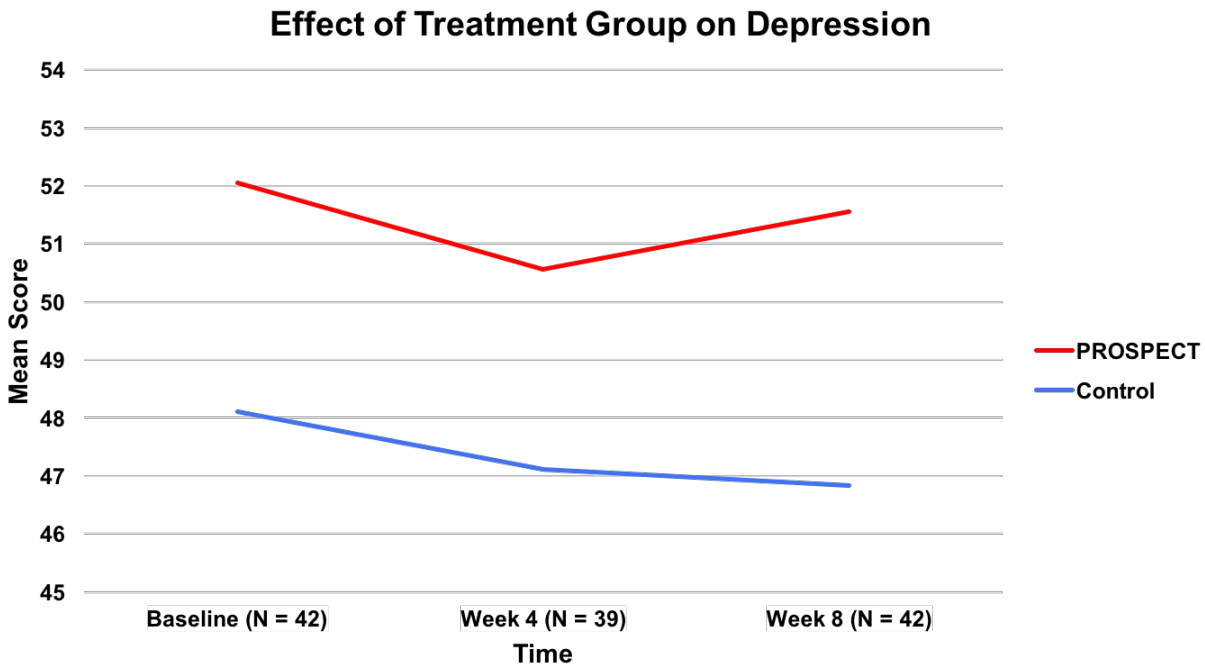


Figure 17

Effect of Treatment on Sleep-related Impairment

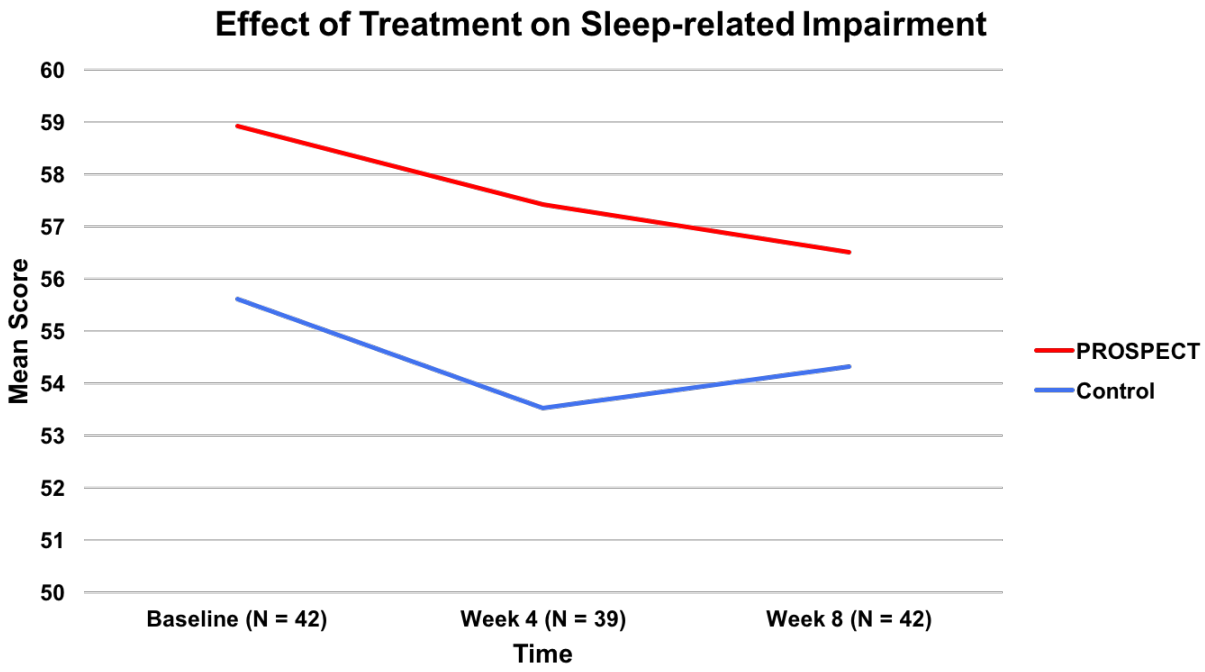


Figure 18

Effect of Treatment and Age on Worst CIPN Pain Intensity

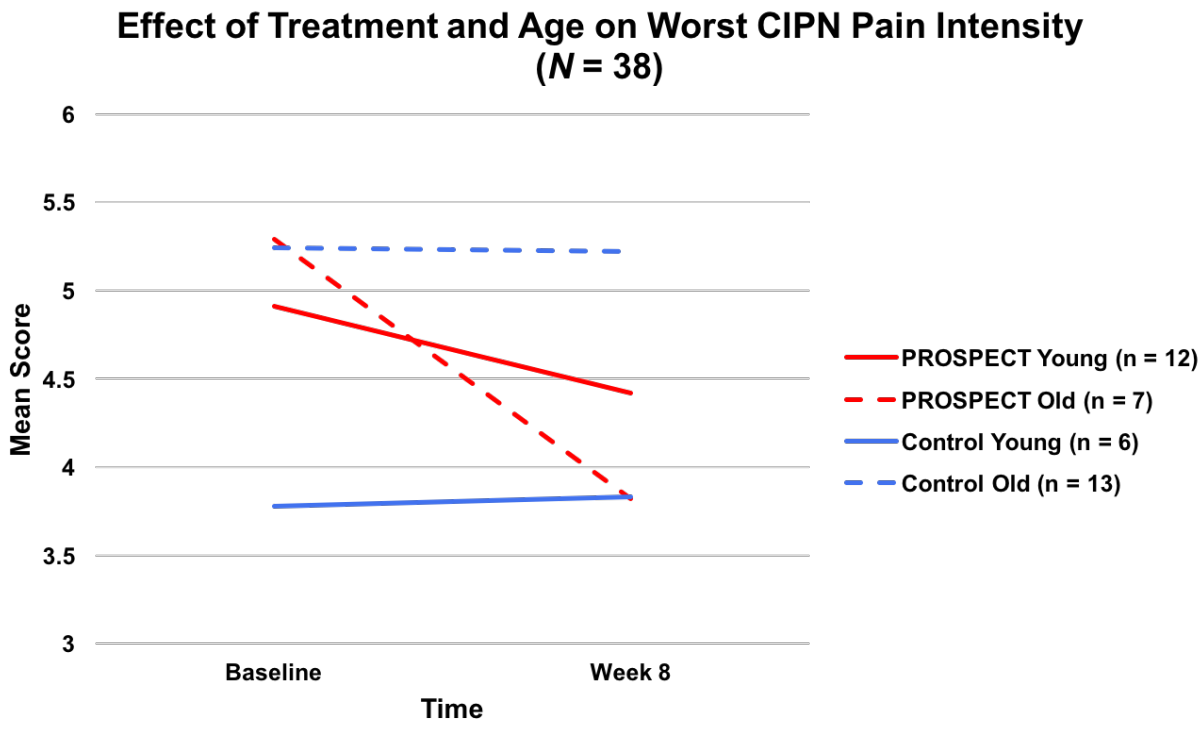


Figure 19

Effect of Treatment and Gender on Worst CIPN Pain Intensity

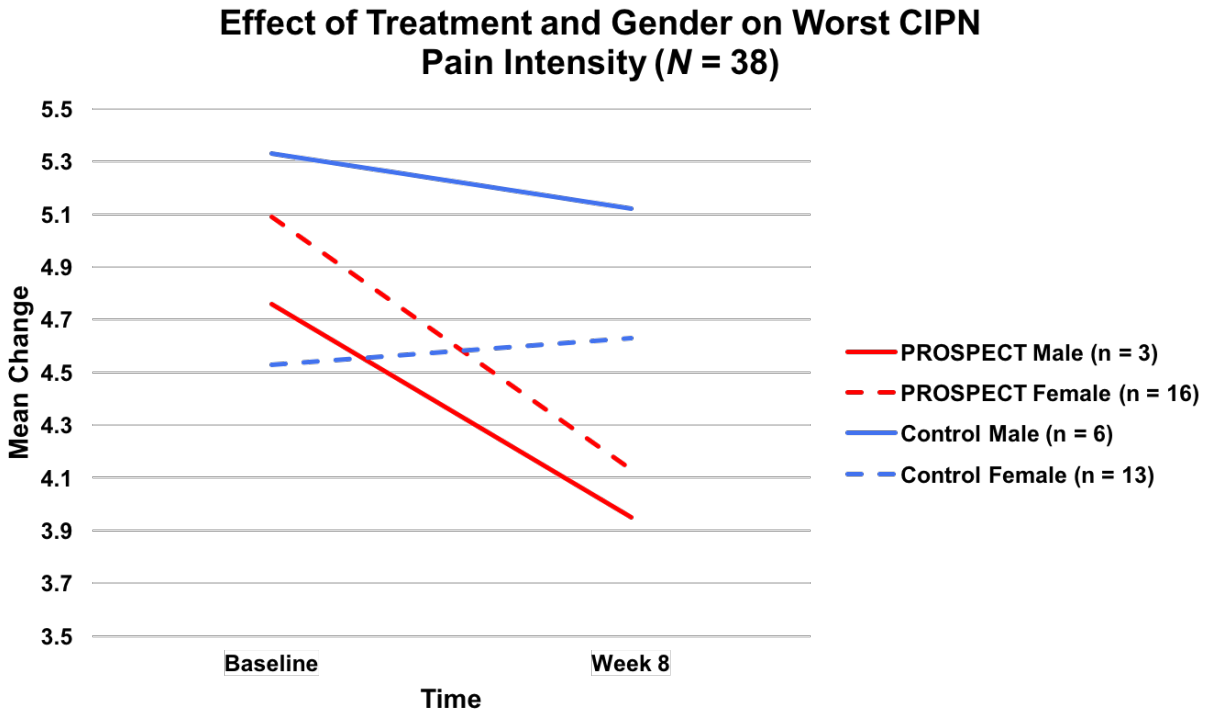


Figure 20

Effect of Treatment and Baseline Depression on Worst CIPN Pain Intensity

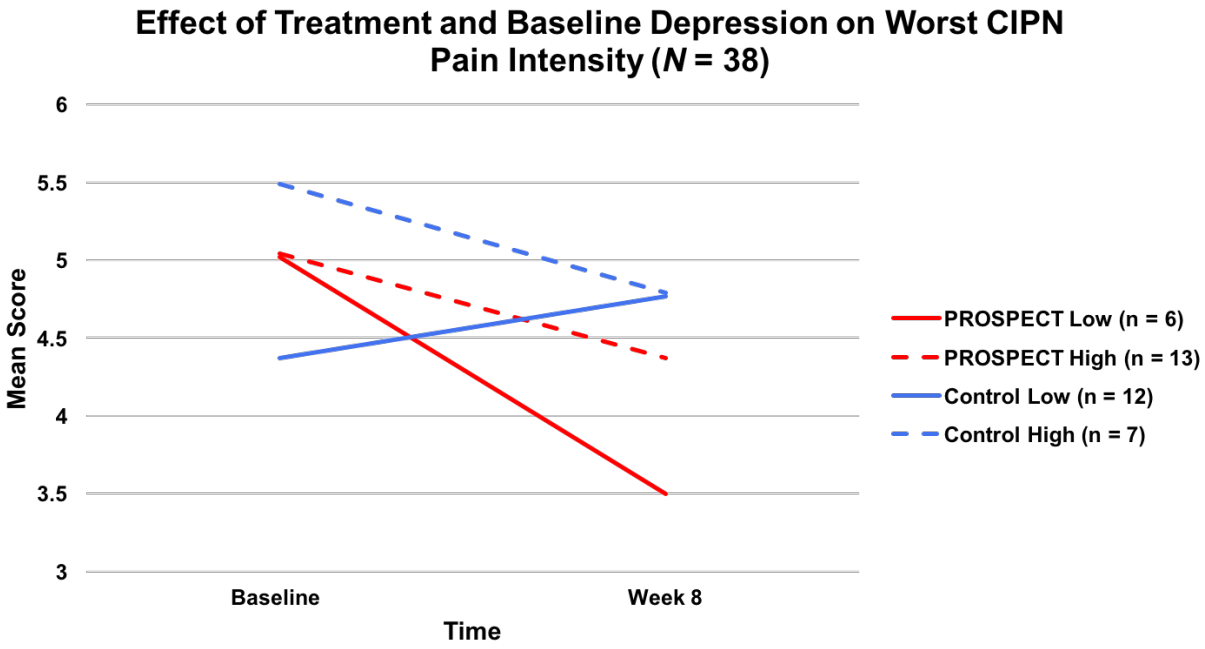


Figure 21

Effect of Treatment and Baseline Pain on Worst CIPN Pain Intensity

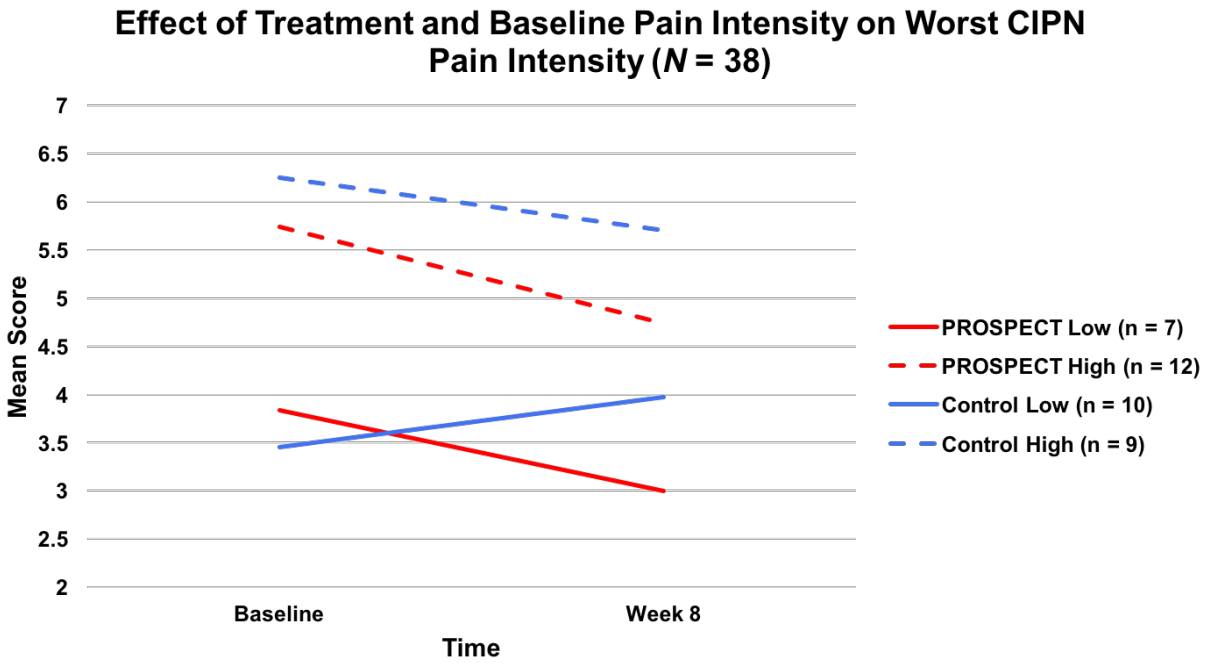


Figure 22

Effect of Treatment and Baseline Anxiety on Worst CIPN Pain Intensity

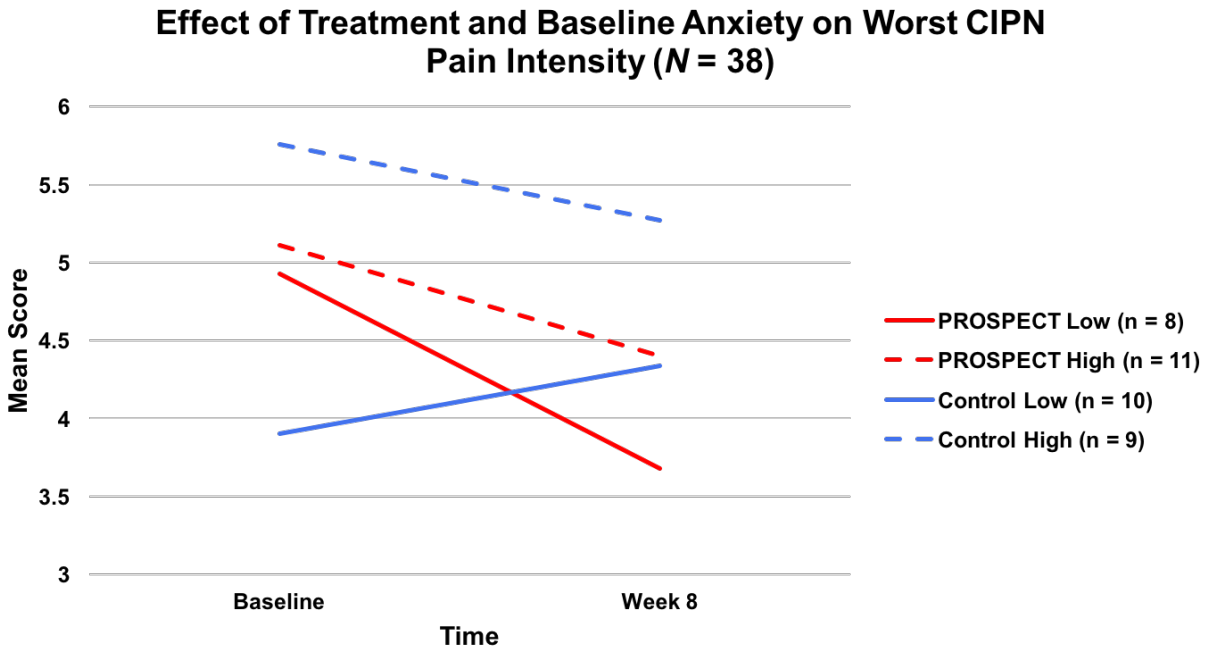


Figure 23

Effect of Treatment and Baseline Fatigue on Worst CIPN Pain Intensity

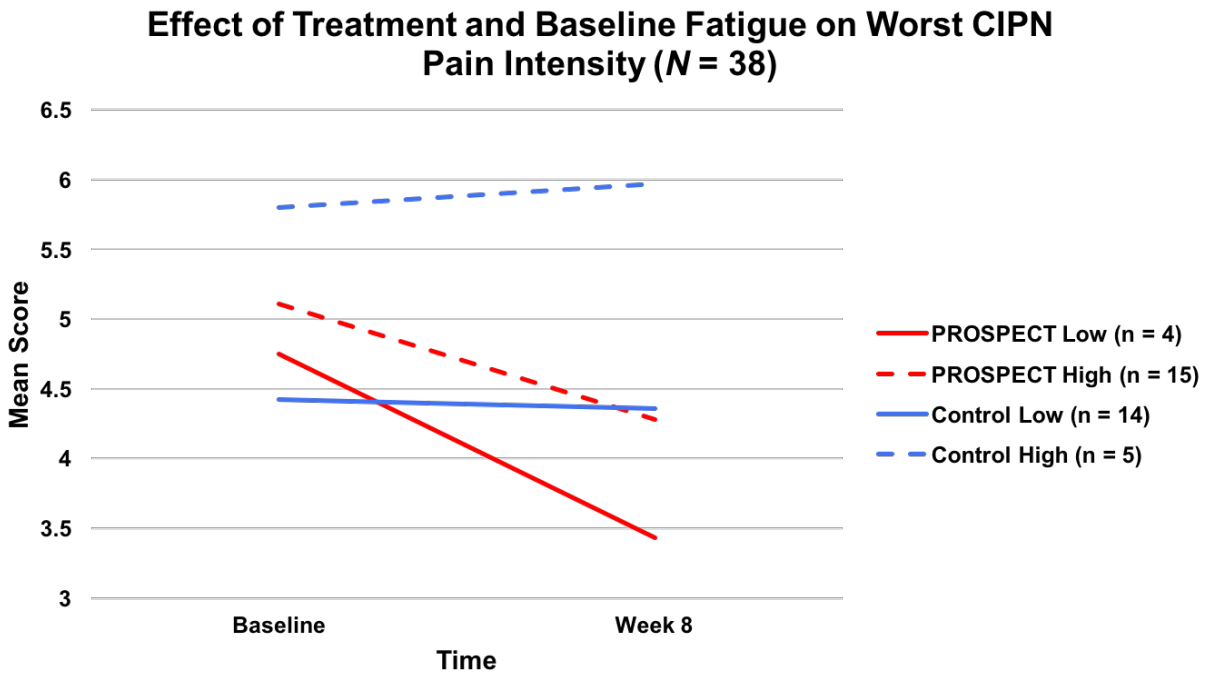
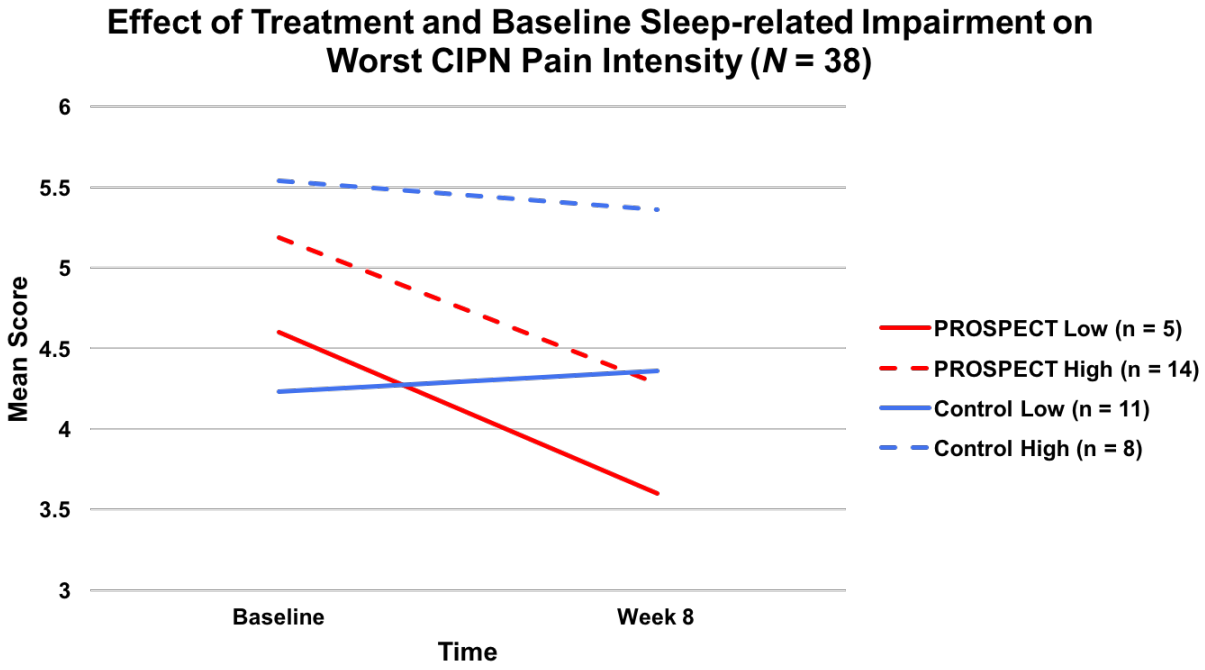


Figure 24

Effect of Treatment and Baseline Sleep-related Impairment on Worst CIPN Pain Intensity



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CHAPTER VI

SUMMARY

Chemotherapy-induced peripheral neuropathy is a common side effect of neurotoxic chemotherapy that is characterized by numbness, tingling, and pain in the extremities (Cavaletti et al., 2013; Kautio, Haanpaa, Kautiainen, Kalso, & Saarto, 2011; Seretny et al., 2014). In a subset of patients with CIPN, painful numbness, tingling, burning, and shooting sensations persist months to years after the completion of neurotoxic chemotherapy (Kolb et al., 2016). The symptoms of painful CIPN decrease patient's quality of life, physical functioning, and require the withdrawal of chemotherapy (Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014; Stubblefield et al., 2009). Despite the negative effect that painful CIPN has on quality of life and physical function, there is only one recommended pharmacological treatment, and no known effective non pharmacological treatments for painful CIPN (Hershman et al., 2014). Thus, the primary purpose of this research was to test the efficacy of a self-guided online cognitive and behaviorally-based pain management intervention (*PROSPECT*) to decrease worst CIPN pain intensity in individuals with chronic (> 3 months) painful CIPN in comparison to individuals receiving treatment as usual. The secondary outcomes were average CIPN pain intensity, pain interference, non-painful CIPN symptoms (e.g., numbness and tingling), and global impression of change. Further, we examined the mediating effect of *PROSPECT*-induced changes in anxiety, depression, fatigue, and sleep-related impairment on worst CIPN pain intensity. Finally, since this intervention has never been tested in individuals with chronic painful CIPN, we assessed patient's ratings of acceptability and satisfaction with *PROSPECT*.

Results

Sample

The study sample consisted of 60 adults with chronic painful CIPN receiving outpatient care at an academic and/or community outpatient cancer center. Specifically, patients had to be experiencing ≥ 4/10 worst CIPN pain intensity for three months since the completion of their neurotoxic chemotherapy regimen. The sample was mainly 61.15 years old, female, Caucasian, college educated, and retired. Ethnic and racial diversity was under-represented in the sample (91.7% Caucasian, 78.3% non-Hispanic). As for cancer-related variables, a wide range of cancer stage was represented in the study population. Additionally, most of the participants had previously received platinum or taxane-based chemotherapy regimens and had breast or gastrointestinal cancers. The most common comorbid illness was hypertension. Individuals receiving *PROSPECT* had considerably higher baseline fatigue and sleep-related impairment severity, otherwise, there were no significant differences between the two study arms (Table 7, Chapter IV). Of the 60 participants, 47 were available for analysis (Aim 1 = 38, Aim 2 = 42, Aim 3 = 37, Aim 4 = 19) (Figure 3, Chapter IV).

Specific Aim 1

The first specific aim was to determine the efficacy of *PROSPECT* in improving worst CIPN pain intensity in individuals with chronic painful CIPN in comparison to individuals receiving treatment as usual.

Findings. Individuals with chronic painful CIPN who received the eight-week *PROSPECT* intervention had a mean change score of -0.94 (*SD* = 1.36, *Range* = -3.29 – 1.29), while individuals in the treatment as usual control group had a mean change score of 0 in worst pain intensity (*SD* = 1.31, *Range* = -3.43 – 2.86). Differences in week eight worst CIPN pain

intensity mean scores between groups was significant when adjusting for baseline scores alone (B = -0.91; p = 0.046; CI = -1.79, -0.02; d = 0.54) (n = 38). When adjusting for age and baseline scores, differences in week eight worst CIPN pain intensity mean scores between groups trended towards significance (B = -0.91; p = 0.058; CI = -1.86, 0.03; d = 0.52) (n = 38). Three (15.8%) individuals in the *PROSPECT* arm reported clinically significant (> 30%) improvements in worst CIPN pain intensity. Overall, *PROSPECT* significantly improved worst CIPN pain in individuals with chronic painful CIPN in comparison to usual care.

This is the first study to test a self-guided online cognitive and behaviorally-based pain management intervention in individuals with chronic painful CIPN. Thus, there are no published comparison studies. However, the findings of this dissertation are consistent with past literature supporting the use of self-guided online cognitive behavioral pain management to improve pain intensity in individuals with chronic pain (Knoerl, Lavoie Smith, & Weisberg, 2015; Macea, Gajos, Daglia Calil, & Fregni, 2010). While we cannot directly compare our results with other self-guided cognitive behavioral trials for painful CIPN, we can compare our results to previous CIPN intervention trials. Currently, only duloxetine 60 mg/day is recommended for the treatment of chronic painful CIPN (Hershman et al., 2014). In a randomized, placebo-controlled crossover trial, Smith et al. (2013) found that duloxetine 60 mg/day resulted in a 1.06 mean decrease in average pain intensity (p = 0.003; d = 0.513) (Smith et al., 2013). While *PROSPECT* had similar mean change scores in pain intensity and effect sizes for the tested interventions, the comparison between duloxetine and *PROSPECT* is complicated because the interventions were tested using two different primary outcomes and duloxetine was tested in a much larger sample (N = 231).

PROSPECT use led to statistically significant, but not clinically significant (>30%) reductions in worst CIPN pain intensity (Farrar, Young Jr, LaMoreaux, Werth, & Poole, 2001).

The overall worst CIPN pain intensity mean change score for individuals receiving *PROSPECT* was -0.94 and only three individuals reported a greater than 30% reduction in pain. While *PROSPECT* significantly improved worst CIPN pain intensity, the results must be interpreted with caution due to the small sample size and the lack of clinically significant improvements.

Specific Aim 2

The second specific aim was to examine the efficacy of *PROSPECT* on average CIPN pain intensity, non-painful CIPN symptoms (e.g., numbness and tingling), pain interference, and global impression of change in individuals with chronic painful CIPN in comparison to individuals receiving treatment as usual.

Findings. There were no significant differences in mean change scores for average pain, pain interference, non painful CIPN symptoms, or the number of individuals reporting improved global impression of change between individuals receiving *PROSPECT* or treatment as usual.

It was surprising that worst pain, but not average pain, improved in individuals receiving *PROSPECT*. One possible explanation for these differences is that we examined worst pain intensity using a seven day diary, whereas we assessed average pain intensity using a single item that asked about pain severity over the past seven days. The use of a single item may not have detected the day to day changes in pain intensity that are common in neuropathic pain states. In addition, we tailored recruitment (i.e. baseline $\geq$ 4/10 worst CIPN pain intensity) to increase assay sensitivity for the primary outcome (worst pain intensity) (Dworkin et al., 2013). Perhaps, if we tailored recruitment to increase assay sensitivity for the secondary aim of average pain intensity, we would have observed greater differences in pain intensity scores between groups. Overall, the differences we observed in worst and average CIPN pain intensity mean change scores may be related to differences in how we measured these variables.

Previous studies testing self-guided cognitive behavioral pain management interventions in individuals with chronic pain have reported improvements in both pain intensity and physical function (Dear et al., 2013; Ruehlman, Karoly, & Enders, 2012; Williams et al., 2010). In addition, physical function and seven-day recall of worst pain intensity are moderately-strongly correlated ($r = 0.65$). Thus, it was surprising that we found that *PROSPECT* improved worst pain intensity, but not pain interference. It is possible that we did not find improvements in pain interference in this current study because while pain improved, patients may still have had functional limitations related to painful numbness and tingling symptoms, which *PROSPECT* may not have adequately addressed. Also, *PROSPECT* usage resulted in statistically significant, but not clinically significant reductions in worst CIPN intensity. Thus, the small improvements in worst CIPN pain intensity (approximately 10%) may not have been great enough to influence pain-related functional impairment

Prior to this current study, there was no evidence to support the use of cognitive behavioral strategies to improve non-painful CIPN symptoms. Study results provide evidence that individuals receiving *PROSPECT* experienced greater improvements in non-painful CIPN symptoms than individuals receiving treatment as usual, however, the difference was not statistically significant. Cognitive behavioral pain management works to improve pain intensity through centrally mediated pain mechanisms (Jensen et al., 2012; Seminowicz et al., 2013), whereas non-painful CIPN symptoms such as peripheral numbness and tingling are a result of peripherally mediated mechanisms (Carozzi, Canta, & Chiorazzi, 2015; Park et al., 2013). However, previous research has demonstrated that non-painful CIPN symptoms are correlated with physiological changes in areas in the brain associated with brain processing (Nudelman et al., 2016). Thus, because cognitive behavioral pain management works to improve pain by

addressing centrally-mediated pain mechanisms, it may also improve non-painful CIPN symptoms via top-down modulation processes. Further research is needed to determine how non-painful CIPN symptoms are processed centrally and if interventions targeting centrally-mediated processes may also improve non-painful CIPN symptoms. The identification of cognitive behavioral strategies or additional interventions that target non-painful CIPN symptoms may lead to further improvements in quality of life and physical function.

Lastly, patients' perceived global impression of change following the completion of the trial did not significantly differ between groups. In comparison to previous research, there have been five recent cognitive behavioral pain management interventions examining patient global impression of change. Results from these trials demonstrated that participant reported significant improvements in impression of change following the course of the intervention (Chiauzzi et al., 2010; McBeth et al., 2012; Monticone et al., 2013; Monticone et al., 2014; Williams et al., 2010). The lack of significant findings in this study may be explained by the small improvement in worst CIPN pain experienced by individuals in the *PROSPECT* group or that individuals were still plagued by additional non-painful CIPN symptoms (e.g., numbness and tingling) that *PROSPECT* may not have adequately addressed.

Specific Aim 3

The third specific aim was to explore the mediating effects of *PROSPECT* induced changes in anxiety, depression, fatigue, and sleep sleep-related impairment on worst CIPN pain intensity in patients with chronic painful CIPN (Aim 3a). Also, we examined the efficacy of *PROSPECT* to improve anxiety, depression, fatigue, and sleep-related impairment in comparison to individuals receiving treatment as usual (Aim 3b). Lastly, as an exploratory aim, we examined

moderators (i.e. age, gender, chemotherapy type, baseline anxiety, depression, fatigue, and sleep-related impairment severity) of worst pain improvement following *PROSPECT* (Aim 3c).

Aim 3a findings. Improvements in anxiety, depression, sleep-related impairment and fatigue mediated nine, zero, seven, and six percent of the total effect of *PROSPECT* on worst CIPN pain intensity, respectively. However, none of these co-occurring symptoms had a statistically significant mediating effect on the primary outcome.

While not significant, our findings are consistent with previous studies demonstrating that emotional factors (i.e., anxiety, depression, and stress) mediate the greatest proportion of the effect of cognitive behavioral pain management on pain intensity in individuals with chronic pain (DasMahapatra, Chiauzzi, Pujol, Los, & Trudeau, 2015; McCracken, Gross, & Eccleston, 2002). There are several possible reasons for the nonsignificant findings in this current study. First, due to low sample size, we were underpowered for our mediation analysis. Second, *PROSPECT* was provided to patients for eight weeks, which may not have been enough time for participants to incorporate the strategies they learned from the website into their daily lives to influence behavior change. Third, because pain, anxiety, depression, fatigue, and sleep-related impairment share common pathophysiological mechanisms, it is possible that improvements in one symptom alone is not enough to correct the shared pathophysiological mechanisms contributing to pain (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010; Boakye et al., 2016; Chao, Mohlenhoff, Weiner, & Neylan, 2014; de Lange et al., 2008; Nudelman et al., 2016; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011; M. T. Smith, Quartana, Okonkwo, & Nasir, 2009). Fourth, worst pain intensity may be mediated through other variables known to influence chronic pain severity that we did not test in this current study. For example, several studies provide evidence demonstrating the role of improvements in catastrophizing as a key

mediator of chronic pain improvement (Seminowicz et al., 2013; Smeets, Vlaeyen, Kester, & Knottnerus, 2006; Turner, Holtzman, & Mancl, 2007).

Aim 3b Findings. Individuals receiving *PROSPECT* experienced greater improvements in anxiety, fatigue, and sleep-related impairment in comparison to individuals receiving usual care. But, there were no statistically significant differences in mean change scores between groups from the baseline to week eight time point.

The lack of statistically significant differences in co-occurring symptom severity between groups may once again be primarily explained by internal validity threats such as small sample size (increased probability of Type II error) and that individuals were provided access to *PROSPECT* for eight weeks (may have not been enough time to influence behavior change). However, there may be additional reasons for the lack of statistically significant differences in co-occurring symptom severity improvement between groups. There are several recent randomized controlled trials supporting the use of self-guided cognitive behavioral pain management for improving anxiety and depression in individuals with chronic pain (Buhrman et al., 2013; Buhrman et al., 2015; Carpenter, Stoner, Mundt, & Stoelb, 2012; Dear et al., 2013, 2015; Ruehlman et al., 2012). We may have found no effect on anxiety or depression in this current study because the intervention may not have contained the appropriate strategies/information to positively impact anxiety and depression. For example, this version of *PROSPECT* did not provide patients with cognitive restructuring strategies, a key component of cognitive behavioral therapy for anxiety and depression (Beck, Beck, & S., 2010). Prior self-guided cognitive behavioral pain management trials that have placed a specific emphasis on cognitive restructuring techniques have been shown to improve anxiety and depression in individuals with chronic pain (Buhrman et al., 2013; Buhrman et al., 2015; Carpenter et al.,

2012; Dear et al., 2013, 2015; Ruehlman et al., 2012). Thus, *PROSPECT* should be modified in the future to include modules focused on cognitive restructuring strategies.

Less is known about the efficacy of self-guided cognitive behavioral pain management for pain-related sleep impairment and fatigue (Williams et al., 2010). This current study demonstrated that individuals using *PROSPECT* experienced modest improvements in sleep-related impairment in comparison to individuals receiving usual care alone. Therefore, because this current version of *PROSPECT* only contained one module devoted to sleep-related impairment, future versions of *PROSPECT* should include additional sleep-related impairment strategies (e.g., sleep restriction, cognitive restructuring) to determine if self-guided online cognitive behavioral pain management can positively impact sleep in individuals with chronic painful CIPN. Further, while *PROSPECT* appeared to have no effect on fatigue in comparison to treatment as usual, there is strong evidence supporting the usage of cognitive behavioral strategies for fatigue (Price, Mitchell, Tidy, & Hunot, 2008). *PROSPECT* should be revised to include additional ways to manage and increase physical activity (e.g., goal setting based on areas of life most affected by fatigue, activity pacing, participating in activities that distract from fatigue) to target fatigue in future *PROSPECT* prototypes (Chan, Yates, & McCarthy, 2016).

Aim 3c Findings. Results of this exploratory analysis revealed that individuals receiving *PROSPECT* with low baseline pain-related symptom severity (i.e. anxiety, depression, fatigue, and sleep-related impairment), older age, and who received taxane-based chemotherapy treatment experienced the greatest improvements in worst CIPN pain intensity.

First, we were not surprised to find that older adults (> 61) experienced greater improvements in worst CIPN pain intensity than younger adults because several studies provide evidence supporting the efficacy of cognitive behavioral interventions for older adults (Berman,

Iris, Bode, & Drengenberg, 2009; Broderick et al., 2014; Keefe, Porter, Somers, Shelby, & Wren, 2013). The difference in pain intensity response to cognitive behavioral pain management may be due to differences in treatment expectations between older and younger adults. Specifically, older adults may have already tried (and failed) a variety of pain interventions and are now more interested in interventions focused on accepting and managing pain intensity (e.g., cognitive behavioral pain management), whereas, younger adults may be more interested in interventions with a curative intent (e.g., medications) (Wetherell et al., 2016).

Second, individuals with lower baseline co-occurring symptom severity (anxiety, depression, fatigue, and sleep-related impairment) experienced greater improvements in worst CIPN pain intensity following *PROSPECT* use than individuals classified in the high severity subgroup. These findings are consistent with a previous study testing duloxetine for chronic painful CIPN, an intervention that also works to improve pain by influencing central nervous system processes. For example, Smith et al. (2015) identified that individuals with high baseline emotional functioning receiving duloxetine were more likely to have a clinically significant improvement in pain intensity than those with low baseline emotional functioning (Smith et al., 2015). An explanation for why individuals with lower baseline co-occurring symptom severity experienced greater improvements in worst CIPN pain intensity may be attributed to shared underlying mechanisms among CIPN pain and co-occurring symptoms. Common pathophysiological mechanisms of pain, anxiety, depression, fatigue, and sleep-related impairment include 1) activation and structural changes in similar brain structures (e.g., prefrontal cortex and limbic system), 2) dysregulation of the HPA axis (e.g., increased cortisol release), 3) alterations in the release of serotonin and norepinephrine (descending pain modulation), and 4) increased pro-inflammatory cytokine release (Barsevick, Frost,

Zwinderman, Hall, & Halyard, 2010; Boakye et al., 2016; Zhuo, 2016). Specifically, individuals with greater co-occurring symptom severity may require a greater cognitive behavioral dose or additional interventions to experience a reduction in pain intensity because they have co-occurring symptoms that exert their maladaptive processes on processes common to pain.

Lastly, individuals with taxane-induced peripheral neuropathy experienced greater improvements in worst CIPN pain intensity following *PROSPECT* use (mean change = -1.46) than individuals with CIPN due to platinum agents (mean change = -0.44). In comparison to previous studies examining chronic painful CIPN treatment response based on CIPN etiology, the results of this study are contrary to previous evidence suggesting that individuals with platinum-induced peripheral neuropathy (mean change = -1.06) respond better to duloxetine 60 mg/day than individuals with taxane-induced peripheral neuropathy (mean change = -0.19) (Smith et al., 2013). However, there is no published evidence demonstrating a relationship between painful CIPN etiology and cognitive behavioral pain management treatment response. While CIPN etiology influences peripheral painful CIPN pathophysiological mechanisms (Carozzi et al., 2015), response to cognitive behavioral pain management treatment should not differ among CIPN etiology because cognitive behavioral pain management does not work through peripheral mechanisms. Thus, the differences in pain response among differing CIPN etiologies may have been related to our small sample size and/or differences in other demographic characteristics among those with differing types of CIPN (e.g., co-occurring symptom severity, gender, age).

Specific Aim 4

The fourth specific aim was to evaluate patients' perceptions of acceptability and satisfaction related to their *PROSPECT* use.

Findings. Overall, acceptability and satisfaction with the study and *PROSPECT* website was moderate to high, with mean Adapted Acceptability E-Scale item scores ranging from 3.26 to 4.58/5. Participants reported that positive features of *PROSPECT* included its ease of use, downloadable worksheets to keep track of symptom severity and strategy use, and access to many symptom management resources. Negative aspects of the *PROSPECT* website included lack of strategies to address non-painful CIPN symptoms (e.g., peripheral numbness and tingling). Barriers to implementing the cognitive behavioral strategies included lack of time and difficulty initiating behavior change on their own. In future versions of *PROSPECT,* participants requested more cognitive strategies related to pain management (e.g., cognitive restructuring) and features to interact with health professionals to discuss symptoms and strategy use. Participants also reported that they thought *PROSPECT* would have been more beneficial if it was offered when they were first beginning their neurotoxic chemotherapy and experiencing CIPN symptoms, not when they already had established painful CIPN symptoms. Overall, the positive feedback adds to the growing body of literature supporting the acceptability and satisfaction of self-guided online cognitive behavioral pain management interventions (Knoerl et al., 2015). Self-guided online cognitive behavioral pain management interventions may be more desirable to patients than in-person delivery methods because the online format addresses several of the barriers associated with in-person delivery (e.g., transportation to the clinic, lack of available trained therapists) (Ehde, Dillworth, & Turner, 2014) by allowing patients to use the strategies of cognitive behavioral pain management as much as they would like without the need to travel to meet with a therapist.

Limitations

There are several limitations of this research. The drop out rate in this study was approximately 22%. This drop out rate is consistent with other self-guided online cognitive behavioral pain management intervention studies (Macea et al., 2010) and the demographic characteristics of the completers and non-completers were similar between groups. However, due to drop out and small sample size, we were not powered to detect differences in the primary (i.e. worst CIPN pain intensity) or secondary outcomes (i.e., pain interference, average CIPN pain, global impression of change, non painful CIPN symptoms, anxiety, depression, fatigue, or sleep-related impairment). Further, due to the high number of individuals with stage IV cancers dropping out of the study, further research is needed to examine the feasibility of administering *PROSPECT* in individuals with advanced cancer.

Due the self-guided nature of the intervention and short duration (eight weeks) of the trial, participants may not have received the optimal dose of the intervention to decrease pain and pain-related symptoms. We may have observed greater improvements in worst CIPN pain and pain-related symptoms if individuals had more time to interact with the strategies of *PROSPECT* because behavior change takes time.

Several differences in baseline characteristics may have confounded the results of the primary analysis. Individuals receiving *PROSPECT* had higher levels of baseline fatigue and sleep-related impairment than individuals in the control group. Despite these differences in co-occurring symptom severity at baseline, individuals receiving *PROSPECT* still experienced greater reductions in worst CIPN pain intensity. Additionally, these differences may have confounded the results related to our analyses examining mean changes in fatigue and sleep-related impairment between groups, but, we did control for baseline co-occurring symptom severity in our analyses. Individuals in the *PROSPECT* group also had greater increases in pain

medications not indicated for the treatment of neuropathic pain and had higher other symptom management activity use than individuals in the control group.

Lastly, we cannot determine if *PROSPECT* usage resulted in greater improvements in pain intensity for individuals with one type of CIPN over another (e.g., platinum vs. taxane-induced) because we examined the *PROSPECT* intervention in individuals who received varying types of neurotoxic drugs. The results are also not generalizable to individuals with low computer literacy or individuals who do not have computer access because the enrolled participants had a high degree of computer literacy.

Recommendations for Future Research

The results of this pilot randomized controlled trial demonstrated that *PROSPECT* had a positive effect on worst CIPN pain intensity, the primary outcome, in individuals with chronic painful CIPN. However, the current study was underpowered, lacked a true placebo control, did not reliably track intervention dose, and did not evaluate the effect of the intervention on the primary or secondary outcomes beyond the end of the intervention period. Based on trends in primary and secondary outcome improvement following *PROSPECT* use and participant feedback, the current version of *PROSPECT* should be revised to include additional cognitive behavioral strategies and to improve the website's interface (usability). Following these revisions, *PROSPECT* should be retested in a larger sample and over a longer time period to truly examine the efficacy of the intervention on pain intensity and co-occurring symptoms.

Several recommendations can be made for the future testing of this intervention in individuals with chronic painful CIPN. First, *PROSPECT* should be revised to add a module that includes cognitive restructuring strategies to address pain and co-occurring symptoms such as anxiety and depression. Revisions may include worksheets/diaries to keep track of automatic

negative thoughts and how to evaluate/challenge these maladaptive cognitions. Additional information should be provided regarding the role of maladaptive cognitions in the maintenance of chronic pain intensity. In addition, future versions of *PROSPECT* should include strategies to address sleep – related impairment (e.g., sleep restriction, cognitive restructuring) and fatigue (e.g., increase in strategies directed at increasing physical activity). Finally, to increase the acceptability and usability of the *PROSPECT* website, several interactive features may be added to increase how enjoyable it is to use the website (e.g., quizzes to test knowledge, clinical vignettes, illustrations, homework, release new information each week, symptom tracking over time, reminders to practice the strategies, and achievement badges or progress checks).

Second, additional research is needed to examine mediators of worst CIPN pain intensity improvement following *PROSPECT* use. Because emotional factors (i.e. anxiety) mediated the greatest proportion of the effect of treatment on worst CIPN pain intensity, these variables should be examined in future studies. In addition, cognitive variables that have been shown to mediate improvements in pain intensity following cognitive behavioral should also be examined within the context of a chronic painful CIPN population (Smeets et al., 2006; Turner et al., 2007). The identification of specific mediators of painful CIPN may allow for further investigation regarding which cognitive behavioral strategies may be most effective in targeting the identified mediators and subsequently relieving CIPN pain intensity.

Third, potential moderators of worst CIPN pain intensity following cognitive behavioral pain management should be examined in future studies testing *PROSPECT*. The current evidence suggests that cognitive behavioral pain management is effective in reducing pain intensity regardless of baseline demographic characteristics (DasMahapatra et al., 2015; Turner et al., 2007). While we found some modest differences in some demographic and cancer

treatment-related variables (i.e., age, low co-occurring symptoms severity), we had a small sample and did not implement any formal statistical tests to assess for differences in pain response between demographic subgroups. Future studies should implement formal statistical tests (logistic regression, multiple linear regression) in a larger sample to evaluate potential moderators of worst CIPN pain intensity following self-guided cognitive behavioral pain management. The identification of moderators of worst CIPN pain intensity improvement will provide the framework for further investigation into who stands to benefit from self-guided cognitive behavioral pain management and when additional intervention may be needed to address co-occurring symptoms to ultimately improve chronic pain intensity.

Fourth, future research can also be directed toward evaluating *PROSPECT* in different patient populations to determine the generalizability of the intervention. In this current study, *PROSPECT* was evaluated in individuals who were mainly Caucasian, non-Hispanic, over the age of 40, and were comfortable using a computer. Little is known about the efficacy of *PROSPECT* for individuals with specific types of CIPN (e.g., related-to taxanes, platinums, vinca alkaloids), low computer/reading literacy, no internet/computer access, or differing racial backgrounds (e.g., African Americans). Targeting recruitment to these specific characteristics in future studies testing *PROSPECT* may increase the generalizability of the intervention and aid in the exploration of additional potential moderators of CIPN pain intensity improvement.

Fifth, if the revised *PROSPECT* intervention demonstrates efficacy in larger studies, *PROSPECT* can be further tested alongside evidence-based treatment for chronic painful CIPN (e.g., duloxetine 60 mg/day) (Smith et al., 2013) to determine 1) if the revised *PROSPECT* intervention significantly improves worst CIPN pain intensity and associated co-occurring symptoms in comparison to treatment as usual, 2) if there are differences in pain response

between individuals receiving *PROSPECT* and duloxetine 60 mg/day, and 3) the synergistic effect of concurrent *PROSPECT* and duloxetine 60 mg/day usage on worst CIPN pain intensity and co-occurring symptoms. The testing of both pharmacological and non-pharmacological interventions for chronic pain is consistent with current clinical practice guidelines for the treatment of chronic pain (Chou et al., 2009).

Lastly, based upon participant feedback, *PROSPECT* may be examined as a preventative modality for chronic painful CIPN. Currently, there are no recommended preventative modalities for the prevention of painful CIPN (Hershman et al., 2014). Thus, *PROSPECT* may be offered when participants are just beginning to receive neurotoxic chemotherapy to determine if the usage of cognitive behavioral strategies delays or prevents the onset of painful CIPN symptoms.

Recommendations for Clinical Practice

The conduct of this randomized controlled trial demonstrates the feasibility of implementing this intervention in individuals with chronic painful CIPN receiving care at clinical outpatient cancer centers. In addition, *PROSPECT* was shown to be efficacious in improving worst CIPN pain intensity. However, *PROSPECT* cannot be currently recommended for the treatment of chronic painful CIPN for a variety of reasons 1) *PROSPECT* usage did not result in clinically significant improvements in any of the tested outcomes, 2) the current study was underpowered, 3) the optimal dose of *PROSPECT* for use in clinical settings is unknown, 4) little is known as to whether *PROSPECT*-induced improvements in pain intensity or co-occurring symptom severity can be sustained beyond the end of the intervention period, and 5) the current study had a high drop out rate, calling into question the feasibility of implementing this intervention for use in specific populations (e.g., individuals with advanced cancers, low computer literacy). With further revisions to the content of the intervention and testing in more

rigorous study designs, *PROSPECT* may eventually be offered as a treatment to supplement evidenced-based pharmacological therapies for the treatment of painful CIPN.

Conclusions

Overall, currently there is one recommended pharmacological agent and no non-pharmacological modalities recommended for the treatment of chronic painful CIPN. In this randomized controlled trial, I tested the efficacy of an eight week self-guided online cognitive and behaviorally-based pain management intervention (*PROSPECT*) in comparison to usual care in individuals with chronic painful CIPN. Results demonstrated that *PROSPECT* significantly improved the primary outcome of worst CIPN pain intensity, but not the secondary outcomes. However, there did appear to be trends in non-painful CIPN symptom severity and sleep-related impairment following *PROSPECT* use. In addition, while anxiety mediated the greatest proportion of the effects of treatment on worst CIPN pain intensity improvements, none of the hypothesized mediators were significant. Due to the small sample size and stated limitations, a larger study is needed to determine the true effect of *PROSPECT* on pain intensity and the secondary outcomes. The identification of mediators of pain intensity improvement in individuals with chronic painful CIPN following self-guided cognitive behavioral pain management will also allow for the targeting of cognitive behavioral strategies to factors known to improve pain intensity. If shown to be efficacious in a larger study, *PROSPECT* should be tested alongside pharmacological agents for the treatment of chronic painful CIPN.

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APPENDICES

Appendix A-1

Table 14

Randomized Controlled Trials Testing Interventions for the Treatment of CIPN

Author	Population	Chemotherapy Type	Intervention and Control	Outcomes	Results	Limitations
Barton et al. 2011	Chronic painful CIPN (*N*=208)	Post-chemotherapy (various)	Intervention: Pluronic lecithin organogel consisting of 10 mg baclofen, 40 mg amitriptyline HCL, and ketamine 20 mg was applied twice a day to areas of painful numbness, tingling, or burning for four weeks Control: Placebo	1. CIPN Severity (Sensory Subscale of the EORTC QLQ-CIPN20^) 2. Mood 3. Pain Intensity (BPI) 4. CTCAE	Participants receiving the intervention had significantly lower EORTC QLQ-CIPN20 motor (p =.021) and sensory subscale (p =.053) scores	1. Approximately 25% of participants dropped out of each treatment arm 2. Less than optimal dose of drug used 3. Patient's feet may have been under-dosed due to the delivery of the treatment 4. The pluronic lecithin organogel may have been the best medium for the topical absorption of the treatment agents

Gewandter et al. 2014	Post chemotherapy CIPN (one month) *(N*=462)	Post chemotherapy (various)	Intervention: Participants could apply up to 4 g of 2% Ketamine/4% amitriptyline cream two times per day to each area with pain/numbness/tingling for six weeks Control: Placebo	1. CIPN pain (seven day average pain/numbness/tingling rating via diary^)	No significant differences between groups	1. Included patients with a pain duration of less than 3 months
Henke et al. 2014	Individuals with lung cancer receiving palliative chemotherapy (*N* = 46)	Platinum-based	Intervention: Conventional physiotherapy + endurance and strength training (over 3 cycles of chemotherapy) Control: Conventional physiotherapy only (breathing exercises and manual therapy)	1. Barthel Index (Activities of daily living) 2. Quality of life (EORTC QLQ-C30)	Significant improvements in the Barthel Index and EORTC QLQ-C30 (e.g., neuropathy p = 0.05, physical function p = 0.03)	1. High dropout rate (63% completed study) 2. Underpowered 3. Did not use strong neuropathy measures
Hirayama et al. 2015	Mix of individuals currently receiving and post chemotherapy (*N* = 34)	Paclitaxel, Oxaliplatin, Vincristine, or Bortezomib	Intervention: Duloxetine 20 mg/day one week, followed by 40 mg/day 3 weeks. Control: Vitamin B12 1.5 mg/day orally for four weeks.	1. Severity of numbness and pain 0 – 10 VAS^	Significant improvements in numbness (p = 0.03) and pain (p = 0.04) in comparison to control	1. Participants were still receiving chemotherapy (CIPN may have resolved or worsened during/after chemotherapy)

					Hazard ratio for nonattainment of >30% reduction in pain was 0.28 in comparison to control.	2. Small sample size (underpowered) 3. Did not explain criteria for study entry related to CIPN severity.
Kautio, Haanpää, Saarto, & Kalso, 2008	CIPN during chemotherapy treatment (*N*=44)	Various	Intervention: Daily (10 mg/day to start then dose was increased by 10 mg/week up to 50 mg/day if tolerated) amitriptyline for eight weeks Control: Placebo	1. CIPN Symptoms (reported pain, numbness, tingling, global improvement, and adverse effects via diary^) 2. Pain Intensity (NPSI) 3. Anxiety 4. Depression 5. Quality of Life	No significant differences between groups	1. Participants had CIPN for less than three months post chemotherapy 2. Study was underpowered (patient recruitment terminated earlier than expected due to low enrollment)
Lindblad, Bergkvist, & Johansson, 2016	Chronic CIPN symptoms (*N* = 67)	Various	Intervention: Weekly interferential therapy and long-wave diathermy at high power for 12 weeks. Control: Long-wave diathermy at low power	1. 0 – 100 NRS of Pain Intensity (post study and 37 weeks post randomization) 2. Nerve Symptoms Drawing 3. Balance testing	No significant differences between groups	1. Underpowered 2. Not all participants had pain at baseline
Lynch et al. 2014	Chronic Painful CIPN (*N* = 16)	Paclitaxel, Vincristine, Cisplatin	Intervention: Cannabis-based spray – up to 12 sprays per day for four weeks. Control: Placebo	1. 0 – 10 NRS of Pain Intensity^ 2. Quality of Life (SF-36) 3. QST	No significant differences between groups	1. Not all participants received same dose 2. Small sample size (underpowered)

Rao et al. 2007	CIPN symptoms for one month (*N*=108)	Post chemotherapy	Intervention: Gabapentin for six weeks (target dose: 2700 mg/day) Control: Placebo	1. Average Daily Pain (NRS^) 2. CIPN severity (ENS Neuropathy Scale^) 3. Pain quality (SF-MPQ) 4. World Health Organization Classification Scale for Neuropathy Symptoms, 5. BPI 6. Global Impression of Change 7. Symptom Distress, 8. Quality of Life 9. Mood	No significant differences between groups.	1. Study was underpowered 2. Heterogeneity of the sample compromised internal validity
Rao et al. 2008	Individuals with CIPN symptoms for at least one month (*N*=131)	Post chemotherapy	Intervention: 300 mg/day lamotrigine for ten weeks Control: Placebo	1. Average Daily Pain (NRS^) 2. CIPN severity (ENS Neuropathy Scale^) 3. Pain quality (SF-MPQ) 4. World Health Organization Classification Scale for Neuropathy Symptoms, 5. BPI 6. Global Impression of Change 7. Symptom Distress, 8. Quality of Life 9. Mood	No significant differences between groups	1. Higher drop out rate in lamotrigine group (33% vs. 18%) 2. Study was underpowered 3. Heterogeneity of the sample compromised internal validity

Rostock et al. 2013	Post chemotherapy with CIPN symptoms (*N* = 60)	Platinums, taxanes, or vinca alkaloids	Intervention: (3 weeks) A) Eight sessions of electroacupuncture B) Eight sessions of hydroelectric baths C) 3 capsules of high dose vitamin B1 and B6 per day (100 mg thiamine nitrate, 100 mg pyridoxine hydrochloride) Control: Placebo	1. Interviews regarding extension and intensity of CIPN symptoms^ 2. Severity of neuropathic symptoms 0-10 NRS^ 3. CTCAE 4. Neuropathy Score (pin sensibility, sensory symptoms, vibratory threshold, strength, reflexes). 5. Sensory nerve conduction tests	No significant differences between groups at end of treatment or follow-up (84 days post randomization).	1. Low CIPN severity at baseline (no minimum baseline CIPN symptom severity inclusion criteria) 2. Underpowered 3. High placebo response
Smith et al. 2013	Chronic painful CIPN (*N*=231)	Post chemotherapy	Intervention: 30 mg of duloxetine for seven days followed by 60 mg of duloxetine for four weeks Control: Placebo	1. Average pain intensity (BPI-SF^) 2. Physical Function (BPI-SF) 3. Quality of Life (FACT/GOG-Ntx-12)	Individuals receiving duloxetine had significantly improved ratings of: 1. Average Pain (p =.003) 2. Physical Function (95% CI: 0.93, 7.88), 3. Quality of Life (p =.03)	1. Higher drop out rate in the duloxetine group (11% vs. 1%). 2. Lack of long-term follow up

Streckmann et al. 2014	Lymphoma (*N*=61)	Neurotoxic and non-neurotoxic chemotherapy	Intervention: 36-week intervention consisting of sensorimotor, endurance, and strength training twice a week (one hour sessions) Control: Treatment as usual	1. Quality of Life (EORTC QLQ-C30^) 2. Peripheral Deep Tissue Sensitivity, 3. Balance Control, 4. Aerobic Performance	Individuals receiving the intervention had significantly improved ratings of: 1. Quality of life at 12 weeks (p =.03) (but not after 36 weeks) 2. Peripheral Deep Tissue Sensitivity (p <.001) 3. Balance control (p =.03) 4. Aerobic Performance (p =.05)	1. Patients had varying underlying cancer diagnoses and not all participants were receiving neurotoxic drug 2. Study was underpowered

Note: BPI-SF = Brief Pain Inventory Short Form, CIPN = Chemotherapy-induced peripheral neuropathy, CTCAE = Common Terminology Criteria for Adverse Events, DEB-NTC = Neurotoxicity Criteria of Debipharm ENS = Eastern Cooperative Oncology Group, EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, EORTC-QLQ-CIPN20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 Chemotherapy-Induced Peripheral Neuropathy 20, FACT-GOG-Ntx-12 = Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group-Neurotoxicity, NPSI = Neuropathic Pain Symptom Inventory, SF-MPQ = Short Form McGill Pain Questionnaire, SF-36 = Short Form-36 Health Survey, QST = Quantitative Sensory Testing, VAS = Visual Analogue Scale.

Appendix A – 2

Table 15

Risk of Bias of Interventions Testing Pharmacological Modalities for the Treatment of CIPN

Author	Adequate Randomization	Concealed Allocation	Sample Size	Similar Groups	Blinded	Measures	Follow-Up	ITT	COI	Risk of Bias
Barton et al. 2011	Y	Y	Y	Y	Y	Y	N	N	?	Low
Gewandter et al. 2014	Y	Y	Y	Y	Y	Y	N	Y	Y	Low
Henke et al. 2014	Y	?	N	Y	?	Y	N	N	Y	High
Hirayama et al. 2015	Y	N	N	Y	N	Y	Y	N	Y	High
Kautio, Haanpää, Saarto, & Kalso, 2008	Y	Y	N	Y	Y	Y	N	N	?	Intermediate
Lindblad, Bergkvist, & Johansson, 2016	Y	?	N	Y	N	Y	Y	Y	Y	Intermediate
Lynch et al. 2014	Y	Y	N	Y	Y	Y	Y	N	Y	Intermediate
Rao et al. 2007	Y	Y	N	Y	Y	Y	N	N	?	Intermediate
Rao et al. 2008	Y	?	N	Y	Y	Y	N	N	?	Intermediate
Rostock et al. 2013	Y	Y	N	Y	N	Y	Y	Y	Y	High
Smith et al. 2013	Y	Y	Y	Y	Y	Y	N	Y	Y	Low

Streckmann et al. 2014	Y	Y	N	Y	N	Y	N	Y	Y	Intermediate

Note: “Y” = Criteria were met; “N” = Criteria were not met; “?” = Insufficient detail, not reported, and/or uncertain if the criteria were met; “ITT” = Did the authors of the study use an intent-to-treat analysis approach? “COI” = Did the authors of the study sufficiently disclose any potential conflicts of interest.

Appendix A – 3

Table 16

Cognitive Behavioral Therapy Randomized Controlled Trials Published 2009-2015

Author	Population	Intervention	Outcomes & Significant Results[a]
Andersson et al. (2012)	Back/Neck (*N*=21)	Intervention: Group CBT; 6 weeks & 12 hours Control: Waitlist	Pain, Quality of Life, Physical Function (PAIRS[a]), Anxiety, Depression, Treatment Satisfaction
Buhrman et al. (2011)	Back/Neck (*N*=54)	Intervention: Online CBT; 12 weeks, self-directed Control: Waitlist	Pain, Catastrophizing[b] (CSQ[a]), Quality of Life (QOLI[a]), Physical Function, Anxiety, Depression
Buhrman et al. (2013)	Back/Neck (*N*=72)	Intervention: Online CBT; 8 weeks, self-directed Control: Online moderated forum	Pain, Catastrophizing[b] (CSQ[a]), Quality of Life, Physical Function (PAIRS[a]), Anxiety (HADS[a]), Depression (HADS[a])
Carmody et al. (2013)	Veterans (*N*= 98)	Intervention: Telephone CBT; 20 weeks, 4 hours Control: Telephone Pain Education	Pain[b], Pain Behavior Checklist[b], CSQ-Revised[b], Quality of Life[b], Depression, Treatment Satisfaction
Carpenter et al. (2012)	Back/Neck (*N*=141)	Intervention: Online CBT; 3 weeks, self-directed Control: Waitlist	Pain, SOPA[a,b], Physical Function, Depression (Negative Mood Regulation Scale[a]), Treatment Satisfaction

Castel et al. (2012)	Fibromyalgia (*N*=93)	Intervention A: Group CBT, B: Group CBT+ Hypnosis; 14 weeks, 28 hours Control: Treatment as usual	Pain (NRS[a]), Physical Function (FIQ[a]), Sleep Disturbance (MOS-Sleep Scale[a]), Anxiety (HADS[a]), Depression (HADS[a])
Chiauzzi et al. (2010)	Back/Neck (*N*=209)	Intervention: Online CBT; 4 weeks, self-directed Control: Pain Education	Pain[b], Physical Function, Anxiety, Depression, Global Impression of Change (PGIC[a])
Christiansen et al. (2010)	Back/Neck (*N*=60)	Intervention: Individual CBT; 9 days, 2 hours Control: Treatment as usual	Pain, Physical Function[b] (Hannover Activities of Daily Living[a])
Dear et al. (2013)	Mixed (*N*=63)	Intervention: Online CBT; 8 weeks, self-directed Control: Waitlist	Pain (BPI[a]), Physical Function[b] (RMDQ[a]), Anxiety[b] (GAD[a]), Depression[b] (PHQ[a]), Treatment Satisfaction
Dunne et al. (2012)	Whiplash (*N*=26)	Intervention: Individual Trauma Focused CBT; 10 weeks, 10 hours Control: Waitlist	Pain, PTSD Symptom Severity[a,b], Mental Health Disorder, Quality of Life (SF-36[a]), Physical Function[b] (Neck Disability Index[a]), Anxiety (DASS[a]), Depression (DASS[a])
Ferrando et al. (2012)	TMD (*N*=72)	Intervention: Group CBT; 12 weeks, 6 hours Control: Treatment as usual	Pain (MPQ-Pain[a]), Physical Function, Anxiety (Brief Symptoms Inventory[a]), Depression (Brief Symptoms Inventory[a])
Glombiewski et al. (2010)	Back/Neck (*N*=128)	Intervention A: Individual CBT, B: Individual CBT+Biofeedback; 8 months, 25 hours Control: Waitlist	Pain[b] (GPQ[a]), Physical Function (PDI[a]), Depression (BDI[a]), Treatment Satisfaction, Global Impression of Change (Did not report *p* value)
Heutink et al. (2012)	Back/Neck (*N*=61).	Intervention: Group CBT; 10 weeks, 30 hours Control: Waitlist	Pain (CPGQ[a]), Quality of Life, Physical Function (CPGQ[a]), Anxiety (HADS[a]), Depression (HADS[a]), Treatment Satisfaction

Jungquist et al. (2010)	Back/Neck (*N*=28)	Intervention: Individual CBT-Insomnia; 8 weeks, 8 hours Control: Face-to-face meetings with nurse therapist	Pain, Physical Function, Fatigue, Sleep Disturbance (ISI[a] & Sleep Diary variables[a]), Depression
Liedl et al. (2011)	Mixed (*N*=36)	Intervention A: Individual CBT+ Biofeedback, B: Individual CBT+ Biofeedback+ Exercise; 10 weeks, 15 hours Control: Waitlist	Pain, Anxiety (HSC[a])
Mangels et al. (2009)	Mixed (*N*=363)	Intervention A: Inpatient Group CBT Rehab, B: Inpatient Group CBT Rehab+booster; Group A = 4 weeks, 13.5 hours, Group B = 4 weeks, 15 hours + 7 sessions over 12 months Control: Treatment as usual	Pain, Physical Function, Quality of Life, Depression (German BDI[a])
Martin et al. (2014)	Fibromyalgia (*N*=110)	Intervention: Group CBT; 6 weeks, 12 hours Control: Waitlist	Pain (FIQ-Pain in last week[a]), Quality of Life (FIQ[a]), Anxiety, Fatigue
Martínez et al. (2014)	Fibromyalgia (*N*=59)	Intervention: Group CBT for Insomnia; 6 weeks, 9 hours Control: Sleep Education	Pain, Physical Function (FIQ[a]), Fatigue (MFI[a]), Sleep Disturbance[b] (PSQI[a]), Depression, Anxiety
McBeth et al. (2012)	Fibromyalgia (*N*=442)	Intervention A: Telephone CBT, B: Exercise only, C: Telephone CBT+Exercise; 7 weeks, 6 hours Control: Exercise only	Pain, Quality of Life (SF-36[a]), Fatigue (Fatigue Scale[a]), Sleep Disturbance (Sleep Scale[a]), Depression, Global Impression of Change[b] (PGIC[a])

Monticone et al. (2012)	Back/Neck (*N*=80)	Intervention: Individual CBT+Exercise; 12 weeks, 10 hours Control: Exercise only	Pain, Quality of Life, Physical Function[b], Treatment Satisfaction
Monticone et al. (2013)	Back/Neck (*N*=90)	Intervention: Individual CBT+Exercise; 12 months, 15 hours Control: Exercise only	Pain (NRS[a]), Quality of Life, Physical Function (RMDQ[a]), Treatment Satisfaction, Global Impression of Change[a]
Monticone et al. (2014)	Back/Neck (*N*=20)	Intervention: Individual CBT+Exercise; 8 weeks, 8 hours Control: Exercise only	Pain (NRS[a]), Quality of Life, Physical Function[b] (ODI[a]), Treatment Satisfaction, Global Impression of Change[a]
Naylor et al. (2010)	Mixed (*N*=51)	Intervention: Group CBT+ 4 months of Therapeutic Interactive Voice Response; 11 weeks, 16.5 hours Control: Treatment as usual	Pain (MPQ- Pain now & Typical[a]), Opioid Medication Intake[ab], Quality of Life (SF-36[a]), Depression (BDI[a]), Treatment Satisfaction
Nicholas et al. (2013)	Mixed (*N*=141)	Intervention: Group CBT; 4 weeks, 16 hours Control: Waitlist	Pain (NRS[a]), Physical Function[b] (RMDQ[a]), Depression (DASS[a]), Treatment Satisfaction
Otis et al. (2013)	Veterans (*N*=20)	Intervention: Individual CBT; 11 weeks, 11 hours Control: Treatment as usual	Pain (MPI-Severity[a]), Physical Function (MPI-Interference[a]), Depression
Pigeon et al. (2012)	Mixed (*N*=21)	Intervention A: Individual CBT for pain, B: CBT for insomnia, C: CBT for Pain/Insomnia; 10 weeks Control: Waitlist	Pain[b], Physical Function, Fatigue, Sleep Disturbance[b] (ISI[a]), Depression[b] (CES-D[a])
Ruehlman et al. (2012)	Mixed (*N*=305)	Intervention: Online CBT; 6 weeks, self-directed Control: Waitlist	Pain (PCP: Screen[a]), Physical Function (PCP: Perceived Disability[a]), Anxiety (DASS[a]), Depression (DASS[a] & CES-D[a])

Sleptsova et al. (2013)	Mixed (*N*=116)	Intervention: Group CBT; 6 months, 37.5 hours Control: Culturally Sensitive Exercise Treatment	Pain, Quality of Life[b], Physical Function, Depression, Treatment Satisfaction
Tang et al. (2012)	Mixed (*N*=20)	Intervention: Individual CBT for Pain/Insomnia; 4 weeks, 8 hours Control: Pain and Sleep Diaries	Pain, Physical Function[b] (BPI-Interference[a]), Fatigue (MFI[a]), Sleep Disturbance[b] (ISI[a]), Anxiety, Depression (HADS[a]), Treatment Satisfaction
Thorn et al. (2011)	Mixed (*N*=83)	Intervention: Group CBT; 10 weeks, 15 hours Control: Pain Education	Pain[b], Quality of Life, Physical Function[b], Depression, Treatment Satisfaction
Van Koulil et al. (2010)	Fibromyalgia (*N*=158)	Intervention A: Group CBT - Pain Persistence+Exercise, B: Group CBT - Pain Avoidance+Exercise; 10 weeks, 32 hours Control: Waitlist	Pain (IGRL-Pain[a]), Physical Function (IGRL-Mobility[a]), Fatigue (Checklist Individual Strength-Fatigue[a]), Anxiety (IGRL-Anxiety[a]), Depression (IGRL-Depression[a])
Vibe et al. (2013)	Back/Neck (*N*=121)	Intervention: Group CFT; 12 weeks, 6 hours Control: Exercise	Pain[b] (NRS[a]), Physical Function[b], Anxiety (HSC[a]), Depression (HSC[a]), Treatment Satisfaction
Vitiello et al. (2013)	Arthritis (*N*= 367)	Intervention: Group CBT- Pain/Insomnia; 6 weeks, 9 hours Control: Education	Pain[b], Physical Function, Sleep Disturbance[b] (ISI[a] & Sleep Efficiency[a])
Williams et al. (2010)	Fibromyalgia (*N*=118)	Intervention: Online CBT; 6 months, self-directed Control: Treatment as usual	Pain[b] (BPI[a]), Physical Function[b] (SF-36[a]), Fatigue, Sleep Disturbance, Anxiety, Depression, Treatment Satisfaction, Global Impression of Change (PGIC[a])
Zachariades (2012)	Mixed (*N*=49)	Intervention: Mailed CBT Manual; 7 weeks, self-directed Control: Education	Pain, Physical Function (PDI[a]), Fatigue (Fatigue Severity Scale[a]), Sleep Disturbance (ISI[a]), Anxiety, Depression

Note: CBT = Cognitive behavioral therapy; PAIRS = Pain and Impairment Relationship Scale; CSQ = Coping Strategies Questionnaire; QOLI = Quality of Life Inventory; HADS = Hospital Anxiety and Depression Scale; SOPA = Survey of Pain Attitudes; NRS = Numerical Rating Scale 0-10; FIQ = Fibromyalgia Impact Questionnaire; MOS-Sleep Scale = Medical Outcomes Study Sleep Scale; PGIC = Patient Global Impression of Change; BPI = Brief Pain Inventory; RMDQ = Roland–Morris Disability Questionnaire; GAD = Generalized Anxiety Disorder-7; PHQ = Patient Health Questionnaire-9; PTSD = Post-Traumatic Stress Disorder; SF-36 = Short Form 36; DASS = Depression Anxiety Stress Scale; TMD = Temporomandibular Disorder; MPQ = McGill Pain Questionnaire; GPQ = German Pain Questionnaire; PDI = Pain Disability Index; BDI = Beck Depression Inventory; CPGQ = Chronic Pain Grade Questionnaire; ISI = Insomnia Severity Index; HSC = Hopkins Symptom Checklist; MFI = Multidimensional Fatigue Inventory; PSQI = Pittsburgh Sleep Quality Index; ODI = Oswestry Disability Index; MPI = Multidimensional Pain Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; PCP = Profile of Chronic Pain; IGRL = Impact of Rheumatic Diseases on General Health And Lifestyle Instrument; CFT = Cognitive Functional Therapy.

[a]Significant result.

[b]Primary outcome.

This table is Table 1 from Knoerl, Smith, & Weisburg (2015).

Appendix A-4

Table 17

Frequency of Cognitive Behavioral Therapy Intervention Strategies

CBT Strategy	Frequency (*n*)	Interventions
Cognitive Restructuring	32	(Buhrman et al. 2011); (Buhrman et al. 2013); (Carmody et al. 2013); (Carpenter et al. 2012); (Castel et al. 2012); (Chiauzzi et al. 2010); (Christiansen et al. 2010); (Dear et al. 2013); (Dunne et al. 2012); (Ferrando et al. 2012); (Glombiewski et al. 2010); (Jungquist et al. 2010); (Liedl et al. 2011); (Mangels et al. 2009); (Martin et al. 2014); (Martínez et al. 2014); (McBeth et al. 2012); (Monticone et al. 2012); (Monticone et al. 2013); (Monticone et al. 2014); (Naylor et al. 2010); (Nicholas et al. 2013); (Otis et al. 2013); (Pigeon et al. 2012); (Ruehlman et al. 2012); (Tang et al. 2012); (Thorn et al. 2011); (van Koulil et al. 2010); (Vibe Fersum et al. 2013); (Vitiello et al. 2013); (Williams et al. 2010); (Zachariades, 2012)
Pain/Psychoeducation	28	(Andersson et al. 2012); (Buhrman et al. 2011); (Buhrman et al. 2013); (Carmody et al. 2013); (Carpenter et al. 2012); (Castel et al. 2012); (Dear et al. 2013); (Dunne et al. 2012); (Ferrando et al. 2012); (Glombiewski et al. 2010); (Heutink et al. 2012); (Liedl et al. 2011); (Mangels et al. 2009); (Martin et al. 2014); (Martínez et al. 2014); (Monticone et al. 2012); (Monticone et al. 2013); (Monticone et al. 2014); (Nicholas et al. 2013); (Otis et al. 2013); (Pigeon et al. 2012); (Sleptsova et al. 2013); (Tang et al. 2012); (Thorn et al. 2011); (Vibe Fersum et al. 2013); (Vitiello et al. 2013); (Williams et al. 2010); (Zachariades, 2012)

Relaxation	21	(Andersson et al. 2012); (Buhrman et al. 2011); (Buhrman et al. 2013); (Carmody et al. 2013); (Carpenter et al. 2012); (Dear et al. 2013); (Dunne et al. 2012); (Ferrando et al. 2012); (Glombiewski et al. 2010); (Heutink et al. 2012); (Liedl et al. 2011); (Mangels et al. 2009); (Martin et al. 2014); (Naylor et al. 2010); (Otis et al. 2013); (Pigeon et al. 2012); (Ruehlman et al. 2012); (Thorn et al. 2011); (Vitiello et al. 2013); (Williams et al. 2010); (Zachariades, 2012)
Activity Pacing	21	(Andersson et al. 2012); (Buhrman et al. 2011); (Buhrman et al. 2013); (Carpenter et al. 2012); (Castel et al. 2012); (Dear et al. 2013); (Ferrando et al. 2012); (Glombiewski et al. 2010); (Mangels et al. 2009); (Martin et al. 2014); (McBeth et al. 2012); (Naylor et al. 2010); (Nicholas et al. 2013); (Otis et al. 2013); (Pigeon et al. 2012); (Ruehlman et al. 2012); (Tang et al. 2012); (van Koulil et al. 2010); (Vibe Fersum et al. 2013); (Vitiello et al. 2013); (Williams et al. 2010);
Relapse Prevention	19	(Andersson et al. 2012); (Buhrman et al. 2011); (Buhrman et al. 2013); (Carmody et al. 2013); (Castel et al. 2012); (Chiauzzi et al. 2010); (Dear et al. 2013); (Dunne et al. 2012); (Ferrando et al. 2012); (Glombiewski et al. 2010); (Jungquist et al. 2010); (Martínez et al. 2014); (McBeth et al. 2012); (Naylor et al. 2010); (Nicholas et al. 2013); (Otis et al. 2013); (Pigeon et al. 2012); (Ruehlman et al. 2012); (Zachariades, 2012)
Exercise	16	(Andersson et al. 2012); (Buhrman et al. 2011); (Buhrman et al. 2013); (Carpenter et al. 2012); (Chiauzzi et al. 2010); (Heutink et al. 2012); (Liedl et al. 2011); (Martin et al. 2014); (Monticone et al. 2012); (Monticone et al. 2013); (Monticone et al. 2014); (Nicholas et al. 2013); (Ruehlman et al. 2012); (van Koulil et al. 2010); (Vibe Fersum et al. 2013); (Williams et al. 2010)
Sleep Hygiene	15	(Andersson et al. 2012); (Buhrman et al. 2011); (Buhrman et al. 2013); (Castel et al. 2012); (Chiauzzi et al. 2010); (Jungquist et al. 2010); (Martínez et al. 2014); (McBeth et al. 2012); (Nicholas et al. 2013); (Otis et al. 2013); (Pigeon et al. 2012); (Tang et al. 2012); (Vitiello et al. 2013); (Williams et al. 2010); (Zachariades, 2012)
Goal setting	13	(Andersson et al. 2012); (Castel et al. 2012); (Chiauzzi et al. 2010); (Christiansen et al. 2010); (Dear et al. 2013); (Glombiewski et al. 2010); (Heutink et al. 2012); (McBeth et al. 2012); (Nicholas et al. 2013); (Otis et al. 2013); (Ruehlman et al. 2012); (van Koulil et al. 2010); (Williams et al. 2010)

Communication/Assertiveness Training	11	(Andersson et al. 2012); (Carmody et al. 2013); (Castel et al. 2012); (Chiauzzi et al. 2010); (Ferrando et al. 2012); (Heutink et al. 2012); (Martin et al. 2014); (Nicholas et al. 2013); (Pigeon et al. 2012); (Thorn et al. 2011); (van Koulil et al. 2010)
Stress Management	11	(Buhrman et al. 2011); (Buhrman et al. 2013); (Carmody et al. 2013); (Carpenter et al. 2012); (Chiauzzi et al. 2010); (Glombiewski et al. 2010); (Heutink et al. 2012); (Liedl et al. 2011); (Monticone et al. 2012); (Monticone et al. 2013); (Monticone et al. 2014);
Stimulus Control	6	(Jungquist et al. 2010); (Martínez et al. 2014); (Pigeon et al. 2012); (Tang et al. 2012); (Vitiello et al. 2013); (Zachariades, 2012)
Sleep Restriction	5	(Jungquist et al. 2010); (Martínez et al. 2014); (Pigeon et al. 2012); (Tang et al. 2012); (Vitiello et al. 2013)
Graded Exposure	5	(Dear et al. 2013); (Dunne et al. 2012); (Tang et al. 2012); (van Koulil et al. 2010); (Williams et al. 2010)
Pleasant Activity Scheduling	4	(Castel et al. 2012); (Dear et al. 2013); (Otis et al. 2013); (Williams et al. 2010);
Managing Medication Use	3	(Naylor et al. 2010); (Williams et al. 2010); (Zachariades, 2012)
Hypnosis	2	(Castel et al. 2012); (Ferrando et al. 2012);
Biofeedback	2	(Glombiewski et al. 2010); (Liedl et al. 2011)
Expressive Writing	2	(Carmody et al. 2013); (Thorn et al. 2011)
Nutrition	1	(Chiauzzi et al. 2010)
Anger Management	1	(Otis et al. 2013)

Note: This table is Electronic Supplementary Table 4 from Knoerl, Smith, & Weisburg (2015).