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Potential mediators of improvement in painful chemotherapy-induced peripheral neuropathy via a web-based cognitive behavioural intervention

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ABSTRACT

Purpose: Preliminary evidence suggests that a self-guided cognitive and behaviourally-based pain management intervention (PROSPECT) is effective for chronic painful chemotherapy-induced peripheral neuropathy (CIPN), but its mechanism of action is unknown. The purpose of this secondary analysis was to explore if changes in anxiety, depression, sleep-related impairment, or fatigue mediated improvements in worst pain following PROSPECT in individuals with chronic painful CIPN.

Methods: Sixty participants were randomized to receive self-guided cognitive behavioural pain management (access for eight weeks) or treatment as usual. A seven-day worst CIPN pain diary and the PROMIS measures of anxiety, depression, fatigue, and sleep-related impairment were administered pre/posttest (eight-weeks). Causal mediation analysis was used to quantify mediators of worst pain improvement.

Results: None of the hypothesized mediators had a statistically significant effect on worst pain ($n=38$).

Implications: Further research is needed to identify potential mediators of pain intensity that can be targeted by specific cognitive behavioural strategies to improve painful CIPN severity.

Key words: chronic pain, chemotherapy-induced peripheral neuropathy, cognitive behaviour therapy, peripheral nervous system disease/chemically induced

INTRODUCTION

Chronic painful chemotherapy-induced peripheral neuropathy (CIPN) occurs in 40% of individuals receiving neurotoxic chemotherapy agents such as platinum or taxanes (Kautio, Haanpää, Kautiainen, Kalso, & Saarto, 2011; Smith, Cohen, Pett, & Beck, 2011). 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 and may negatively affect quality of life and/or physical function (Beijers, Mols, Dercksen, Driessen, & Vreugdenhil, 2014; Smith et al., 2014).

Currently, there is only one pharmacological (duloxetine 60 mg/day) and no non-pharmacological treatment recommended for the management of chronic painful CIPN (Hershman et al., 2014; Smith et al., 2013). A recently conducted randomized, waitlist-controlled trial (Knoerl, Smith, et al., 2017) examined the efficacy of a self-guided online cognitive and behaviourally-based pain management intervention called Proactive Self-Management Program for Effects of Cancer Treatment (PROSPECT) on worst CIPN pain severity. Results demonstrated that PROSPECT usage significantly reduced worst pain intensity in comparison to individuals receiving usual care ($p = 0.046$). Despite the statistically significant findings, 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 behavioural pain management works to improve painful CIPN. Thus, further research is needed to identify mediators of pain intensity that can be targeted by PROSPECT to improve the intervention's effect on painful CIPN severity.

Numerous studies provide evidence supporting the relationships between several mediating variables and chronic painful CIPN intensity (i.e., anxiety, depression, fatigue, and sleep-related impairment (Hershman et al., 2016; Smith et al., 2015). Further, these relationships are supported by shared underlying pathophysiological mechanisms: 1) neurobiological changes (Boakye et al., 2016; Nudelman et al., 2016; Zhuo, 2016), 2) pronounced stress response (e.g., disruption of the hypothalamic-pituitary-adrenal axis), 3) cytokine dysregulation, and 4) 5-HT and norepinephrine dysregulation

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(Barsevick, Frost, Zwiderman, Hall, & Halyard, 2010; Boakye et al., 2016). Cognitive behavioural 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 nor-epinephrine and serotonin (Jensen et al., 2012; Seminowicz et al., 2013). Thus, because chronic painful CIPN co-occurs with symptoms that share similar pathophysiological mechanisms and cognitive behavioural 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. However, we are unaware of published studies that have examined mediators of chronic painful CIPN pain intensity improvement following self-guided cognitive behavioural pain management. The purpose of this secondary analysis was to explore the mediating effect of mean changes in sleep-related impairment, anxiety, depression, or fatigue on worst pain intensity following PROSPECT in individuals with chronic painful CIPN.

MATERIALS AND METHODS

Design, Setting, and Sample

This current study was a secondary analysis of a pilot, randomized, wait-list controlled trial testing the effect of PROSPECT on worst CIPN pain intensity in comparison to individuals receiving treatment as usual (Knoerl et al., 2017). Briefly, 60 patients with chronic painful CIPN (e.g., $\geq 4/10$ worst CIPN pain for ≥ 3 months since completion of neurotoxic chemotherapy) were recruited from five academic and/or community outpatient cancer centres over six months. Patients were excluded if they had neuropathy due to other causes or planned to receive neurotoxic chemotherapy at any point during the study. The study protocol was approved by the study sites' Institutional Review Board and enrolled participants provided written informed consent.

Measures

An 11-point numerical rating scale ("10" represents worst pain imaginable) was used to measure worst CIPN pain severity (Cleeland & Ryan, 1994) and was administered via a seven-day diary at the baseline and eight-week time points. Participants' responses from the seven-day diary were averaged at the respective time points. In addition, various Patient Reported Outcome Measurement Information System (PROMIS) measures were used to quantify anxiety, depression, fatigue, and sleep-related impairment in the recruited sample (Cella et al., 2007). The PROMIS Anxiety 4a (four items; 1 = never; 5 = always; transformed total score range 40.3–81.6) measures self-reported fearfulness, worry, and uneasiness over the past seven days (Kroenke, Yu, Wu, Kean, & Monahan, 2014). The PROMIS Emotional Distress-Depression 4a (four items; 1 = never; 5 = always; transformed total score range 41.0–79.4) examines patient reported sadness, self-perception, loneliness, and self-purpose over the past seven days (Bartlett et al., 2015; 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/personal roles (Bartlett et al., 2015). The 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 (Yu et al., 2012).

Procedures

At baseline, prior to randomization, participants completed the first day of the seven-day worst CIPN pain diary and the PROMIS subscales via computer tablet. The principal investigator then randomized participants to a study group (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 (to complete the remaining six days of the diary) and submitted their scores via an emailed survey link. Following completion of the pain diary, participants were emailed the link to the PROSPECT website or information about the treatment as usual control group. The PROSPECT website contains cognitive behavioural strategies (e.g., activity pacing for fatigue, progressive muscle relaxation/deep-breathing for anxiety/depression, sleep hygiene strategies for sleep-impairment) and self-management information (e.g., patient-provider communication about symptoms and goal setting) designed to help individuals manage cancer treatment-related symptoms. The content is delivered via written information and videos. The PROSPECT intervention also recommends different modules and strategies based on the participants self-reported symptoms. Participants were trained by the principal investigator at baseline about how to access/use the PROSPECT website and were encouraged to use the PROSPECT website at their discretion. Eight weeks following randomization, participants were emailed electronic versions of the seven-day worst CIPN pain intensity diary and PROMIS measures.

Statistical Analyses

R version 3.4.0 was utilized to analyze all data (R Development Core Team, 2017). The sample analyzed was based on individuals who completed all pre/posttest survey data in the primary study. There were 38 individuals who provided complete baseline and week eight worst CIPN pain intensity in the primary study (Knoerl et al., 2017), but only 37 of those individuals provided complete data for the secondary outcomes explored in this study (< 5% missing data for this analysis). To be consistent with the sample size of the primary study, we used mean imputation to handle missing data for one participant (Little, Jorgensen, Lang, & Moore, 2014). We did not conduct an a priori power analysis due to the exploratory nature of this analysis.

Causal mediation (Imai, Keele, & Tingley, 2010) was used to explore if changes in anxiety, depression, fatigue, or sleep-related impairment mediated the effects of PROSPECT on worst pain intensity improvement over the eight-week treatment period (Figure 1). 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 1) (Imai et al., 2010). The indirect effect can be further defined as the

Figure 1. Hypothesized Mediation Model of PROSPECT on Worst CIPN Pain Intensity
 This figure describes the hypothesized mediators of the effect of PROSPECT on worst CIPN pain intensity. 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.

change in the outcome (i.e., worst pain) when the value of the mediator (e.g., anxiety) is changed from the value reported by the control to the value reported by the treatment.

Descriptive statistics (mean, SD) were calculated for all continuous data at the baseline and week eight time points (i.e., worst CIPN pain, fatigue, anxiety, depression, and sleep-related impairment). Next, to assess the effect of PROSPECT on the hypothesized mediators, week eight mean scores in anxiety, depression, sleep-related impairment, and fatigue were compared between groups using ANCOVA adjusting for baseline scores. If results showed that PROSPECT had no effect on a hypothesized mediator, then mediation analyses could not be conducted because a variable can only be a mediator of an outcome when it is significantly affected by the treatment (Imai et al., 2010). Subsequently, for variables that demonstrated a statistically significant improvement following PROSPECT use, we modelled: 1) the mediators (anxiety, depression, fatigue, and/or sleep-related impairment week eight scores, respectively) given the treatment and baseline covariates (i.e., baseline worst pain scores), and 2) the outcome (worst pain intensity week eight 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., 2014) package to estimate the causal mediation effect and 95% CI of the causal mediation effect for each mediation model.

RESULTS

Sample Characteristics

The demographic and cancer treatment-related characteristics of the recruited sample have been previously described (Knoerl, Smith, et al., 2017). 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 (43.3%), married (70%), and regularly used a computer (85%). Additionally, most participants had breast (38.3%) or gastrointestinal (43.3%) cancers and had varying cancer severity. Individuals receiving PROSPECT had more severe fatigue and sleep-related impairment at baseline in comparison to individuals receiving treatment as usual. Also, individuals who did not complete the study had more advanced cancer severity (46% had Stage IV cancer in comparison to 19% for completers), but, there were no considerable differences in baseline pain or co-occurring symptom severity between completers and non-completers.

Mediation Analysis

Table 1 describes mean scores for the variables of anxiety, depression, fatigue, and sleep – related impairment at the baseline and week eight time points. There were no significant differences in anxiety, fatigue, sleep-related impairment, or depression severity between groups at the week eight time point ($p > 0.05$, $n = 38$). Trends in anxiety, depression, and fatigue 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. Nevertheless, because PROSPECT did not have a statistically significant effect on the hypothesized mediators in comparison to the treatment as usual control group, mediation analyses could not be conducted.

DISCUSSION

The results of the mediation analyses revealed that none of the hypothesized influencing factors of chronic painful CIPN significantly mediated worst CIPN pain intensity improvement following PROSPECT. Published studies have demonstrated that emotional factors mediate pain intensity improvement following in-person (i.e., anxiety) and online (i.e., stress and depression)

Table 1. Mean PROMIS Subscale Scores at the Baseline and Week Eight Time Points			
Outcomes (n = 38) ^a	Intervention Mean (SD)	Wait-List Control Mean (SD)	Contrast Between Groups ^a
Sleep-related Impairment			
Baseline	58.74 (6.65)	55.84 (5.38)	B = 0.22; p = 0.87; CI = -2.39, 2.82
Week Eight	56.71 (5.90)	54.34 (5.86)	
Fatigue			
Baseline	59.59 (6.55)	53.31 (7.84)	B = 0.22; p = 0.92; CI = -3.90, 4.33
Week Eight	56.83 (8.41)	51.47 (7.92)	
Depression ^b			
Baseline	52.79 (7.03)	47.89 (7.12)	B = 2.54; p = 0.16; CI = -1.03, 6.11
Week Eight	52.14 (6.89)	46.73 (6.13)	
Anxiety			
Baseline	54.45 (7.27)	50.09 (7.82)	B = 1.38; p = 0.55; CI = -3.23, 5.99
Week Eight	52.62 (8.59)	48.63 (7.41)	
This table describes differences in week eight mean scores for the variables of sleep-related impairment, fatigue, depression, and anxiety between individuals receiving PROSPECT or treatment as usual (Wait-List Control)			
^a Difference in Week Eight mean scores adjusting for baseline scores			
^b Individuals receiving usual-care experienced greater improvements			

cognitive behavioural pain management (DasMahapatra, Chiauuzzi, Pujol, Los, & Trudeau, 2015; McCracken, Gross, & Eccleston, 2002). One reason as to why anxiety and depression were not observed as mediators in this current study 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, 2010). Cognitive restructuring has been demonstrated to be a key component of previous self-guided cognitive behavioural pain management interventions. Of the seven-self-guided cognitive behavioural pain management trials reviewed by Knoerl, Lavoie Smith, & Weisberg (2015), four had positive effects on anxiety/depression. These four trials placed a specific emphasis on cognitive restructuring by providing participants with access to modules containing this strategy for multiple weeks. Conversely, programs that focused more on self-management (e.g., communication with provider, medication management, goal setting) alone 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 (Knoerl, Lavoie Smith, & Weisberg, 2015). 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 behavioural 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 (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.

While we assessed the mediating effect of anxiety, depression, fatigue, and sleep-related impairment on worst CIPN pain intensity, 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 (Seminowicz et al., 2013; Turner, Holtzman, & Mancl, 2007). 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) (Beck, 2010) to target cognitive variables such as catastrophizing in subsequent studies.

IMPLICATIONS

The nature of this research has several implications for clinical nurses. Despite the negative results of this study, nurses should continue to encourage self-management strategy use in individuals with cancer treatment-related symptoms. Specifically, an integrative review by Hammer et al. (2015) reviewed 46 articles testing self-management interventions for individuals with cancer (all studies led by nurse-scientists) and reported that several of the reviewed self-management interventions had positive effects on cancer treatment-related symptoms (e.g., pain, fatigue, depression, anxiety) (Hammer et al., 2015). Further, self-management strategies are associated with no notable side effects and can be administered concurrently with standard treatments. However, before delivering self-management strategies, nurses must assess their patients' willingness and ability to self-manage symptoms. Subsequently, nurses must select self-management strategies that coincide with their patients' preferences/abilities and schedule (e.g., appointments, treatments, personal life) (McCorkle et al., 2011).

LIMITATIONS

There are several limitations to this study. The study was underpowered, which may increase the probability of finding a false negative result (Type II error). 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 behaviour change related to pain management. Similarly, due to the self-guided nature of the intervention, perhaps participants did not receive the optimal dose of the intervention to decrease pain-related symptoms. Lastly, while we collected data related to the amount of time participants said they spent using PROSPECT each week (Knoerl et

al., 2017), we did not collect data about how often participants spent using specific modules within PROSPECT. Thus, it is possible that participants did not routinely use the modules containing strategies related to anxiety, depression, fatigue, and/or sleep-related impairment. Despite these limitations, the results of this study contribute to the growing body of literature surrounding the identification of mediators of pain intensity improvement following cognitive behavioral pain management to gain a greater understanding of how this treatment may work to improve pain.

CONCLUSION

In conclusion, 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. Further, perhaps the PROSPECT intervention should be modified in the future to amplify its effect on potential mediation targets. The identification of mediators of pain intensity in individuals with painful CIPN will allow for the targeting of behavioral strategies to factors known to improve pain intensity.

DISCLOSURES

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