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

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Abstract: **The purpose of this pilot, parallel, randomized controlled trial was to examine the efficacy of a self-guided online cognitive and behaviorally-based pain management intervention (Proactive Self-Management Program for Effects of Cancer Treatment [PROSPECT]) to reduce "worst" pain for individuals with chronic painful chemotherapy-induced peripheral neuropathy (CIPN). Secondary outcomes included "average" pain, nonpainful CIPN symptom severity, impression of change, and pain interference. Sixty patients with chronic painful CIPN were recruited from 5 outpatient academic and community cancer centers. Patients were randomized in a 1:1 ratio to receive either 8 weeks of PROSPECT or usual care. A 7-day electronic "worst" pain intensity diary and standardized measures of pain interference, nonpainful CIPN symptom severity, impression of change, and "average" pain were administered pre/post intervention. Postintervention mean scores were evaluated between groups using analysis of covariance adjusting for baseline. Individuals who received the PROSPECT intervention (n = 19) had significantly greater improvements in "worst pain" compared with individuals receiving usual care (n = 19; *P* = .046, d = .58). There were no significant differences in mean scores between groups for the secondary outcomes (n = 42). 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.**

Perspective: ***This study explores the efficacy of an 8-week online cognitive behavioral pain management intervention for chronic painful CIPN. Intervention use resulted in greater improvements***

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in "worst" pain than usual care alone. The findings provide preliminary support for the efficacy of a nonpharmacological intervention for chronic painful CIPN.

Key words: *Chronic pain, chemotherapy-induced peripheral neuropathy, cognitive-behavioral therapy, peripheral nervous system disease/chemically induced.*

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer treatment that can occur in up to 68% of individuals receiving neurotoxic chemotherapy (eg, platinums, bortezomib, and taxanes).[6,31,51] The symptoms of CIPN include numbness, tingling, and pain in the hands and/or feet (symptoms generally present in a symmetrical, stocking-glove distribution).[53] In up to 40% of patients,[31,62] CIPN may become chronically painful and persist for months to years after the completion of chemotherapy.[18,39,56] Patients with painful CIPN often report decreases in quality of life and physical function and may be required to stop potentially life-saving neurotoxic chemotherapy regimens.[42,57]

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/d is currently the only medication recommended for the treatment of painful CIPN.[24,54] Because of their efficacy in other neuropathic pain populations, antidepressants and anticonvulsants are often used to treat painful CIPN.[24] However, adherence to these types of medications is poor because of side effects or lack of efficacy.[20] Use of an effective, nonpharmacologic intervention for painful CIPN may decrease the need for drug therapy—potentially reducing the overall side effect burden for cancer survivors and/or create a synergistic pain-reducing effect by the use of multiple modalities. Thus, multimodal management approaches that incorporate nonpharmacologic approaches for painful CIPN warrant further study.

One nonpharmacologic treatment used commonly for the treatment of chronic pain (eg, back/neck, musculoskeletal, and fibromyalgia) is therapist-administered cognitive-behavioral pain management.[7,40,46,61,64] 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, sleep hygiene, activity pacing, and cognitive restructuring.[17,32] Cognitive-behavioral pain management may reduce pain intensity by inducing structural changes in the prefrontal cortex (eg, increased gray matter volume).[27,50] 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 (eg, norepinephrine and serotonin) that influence descending pain inhibition mechanisms.[27,50] 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.[17,34] One way to overcome these barriers is to offer this treatment in a self-guided online 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.[9,34,38,65] However, little is known about the efficacy of self-guided cognitive-behavioral pain management for chronic painful CIPN.

Purpose

The purpose of this randomized, wait-list control pilot study was to test the efficacy of a self-guided cognitive-behavioral 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 compared with individuals receiving treatment as usual (ClinicalTrials.gov Identifier: NCT02760654). Secondarily, we explored the efficacy of the PROSPECT intervention to improve CIPN symptom severity (eg, nonpainful numbness and tingling), pain interference, average pain severity, and patients' perceived global impression of change. Last, we explored participant acceptability of and satisfaction with PROSPECT.

Methods

Design, Setting, and Sample

The study aims were examined via a parallel, 1:1 randomized controlled trial design. Sixty patients were recruited from 5 outpatient community and/or academic oncology clinics in Southeast Michigan. Patients were eligible if they: 1) were older than 25 years of age, 2) self-reported ≥4 of 10 worst CIPN pain that persisted 3 months or longer after the cessation of neurotoxic chemotherapy, 3) had at least National Cancer Institute Common Terminology Criteria for Adverse Events grade 1 sensory CIPN,[44] 4) had a stable analgesic medication regimen (≤10% change in dosage in the 2 weeks before study enrollment), and 5) were able to access/use a computer. Participants were excluded if they had: 1) a prognosis of <3 months, 2) peripheral neuropathy from 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 8 weeks of PROS-