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

Robert Knoerl,* Ellen M. L. Smith,† Debra L. Barton, † David A. Williams, ‡ Janean E. Holden, † John C. Krauss, § and Beth LaVasseur ¶

*Phyllis F. Cantor Center for Research in Nursing and Patient Care Services, Dana-Farber Cancer Institute, Boston, Massachusetts.
†School of Nursing, University of Michigan, Ann Arbor, Michigan.
‡School of Medicine, University of Michigan, Ann Arbor, Michigan.
§Comprehensive Cancer Center, University of Michigan, Ann Arbor, Michigan.
¶St. Joseph Mercy Hospital, Ann Arbor, Michigan.

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...
The symptoms of CIPN include numbness, tingling, and pain in the hands and/or feet (symptoms generally present in a symmetrical, stocking-glove distribution).\(^{15}\) In up to 40% of patients,\(^ {10,51}\) CIPN may become chronically painful and persist for months to years after the completion of chemotherapy.\(^ {18,59}\) 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.\(^ {12,57}\)

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.\(^ {25}\) 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.\(^ {17,40,46,61,64}\) 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-
PECT or treatment as usual (control) in a 1:1 ratio using a computer-generated random numbers table. Randomization was stratified according to 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. After informed consent and completion of all baseline assessments, participants were informed of their study group assignment. After the administration of the baseline assessments by the principal investigator, trained study staff administered all data collection procedures at the subsequent time points. Health care providers were not informed of their patients’ study group assignment.

PROSPECT

The password-protected PROSPECT Web site contained cognitive-behavioral pain management strategies and information designed to help individuals manage pain and co-occurring symptoms after cancer treatment (eg, anxiety, depression, sleep, fatigue, and impaired cognition). Content (10 modules; Table 1) is presented using written as well as video formats and patients can download worksheets further describing the strategies. At baseline, participants were trained on how to navigate the PROSPECT Web site and were encouraged to complete the “Steps for Me” link, which recommends modules on the basis of the patient’s responses to questions about symptom severity and symptom management practices. Participants were instructed to use the modules as much as they desired and did not receive any additional encouragement from the study staff after obtaining access to the PROSPECT Web site.

Wait-List Control

Participants in both groups continued to receive their usual care from their primary provider (eg, routine oncology follow-up appointments and subspecialty appointments). Participants randomized to the control group received access to the PROSPECT Web site after the completion of all required surveys.

Measures

An 11-point numeric 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). The 11-point worst CIPN pain NRS was administered within a 7-day pain diary pre/post intervention, whereas the average CIPN pain NRS was administered via a single item asking about average CIPN pain severity over the past 7 days (worst pain was assessed in similar fashion at week 4). Participants were coached to only report pain resulting from CIPN (eg, painful numbness, tingling, burning in hands/feet), not pain from other sites or causes. The 11-point NRS is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and several trials have supported its reliability and validity. On the basis of evidence suggesting that worst pain intensity is more highly correlated with average functional interference than average current or current pain intensity, worst pain intensity was selected as the primary outcome.

Several other comorbid 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 (4 items; 1, not at all; 5 very much; transformed total score 41.6–75.6) subscale measures the effect of pain on the social, cognitive, and physical aspects of one’s life over the past week. There is strong evidence supporting the reliability and validity of the PROMIS pain interference item bank. In addition, to measure impression of change after completion of the trial, we used the Patient Global Impression of Change (PGIC). The PGIC is a self-report item designed to assess patients’ overall impression of improvement over the course of a clinical trial.

Table 1. Summary of PROSPECT Modules

<table>
<thead>
<tr>
<th>Module</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>About Late Effects</td>
<td>Education about common cancer treatment-related side effects (ie, pain, fatigue, problems with memory, emotional distress, sleep problems)</td>
</tr>
<tr>
<td>Talk to Your Team</td>
<td>Strategies to promote communication between the patient and their provider regarding cancer treatment-related symptoms</td>
</tr>
<tr>
<td>Get Your Body Moving</td>
<td>Benefits of physical activity during cancer treatment and provides strategies to start and maintain regular physical activity</td>
</tr>
<tr>
<td>Get a Better Night’s Sleep</td>
<td>Sleep hygiene strategies to help individuals fall and stay asleep at night</td>
</tr>
<tr>
<td>Slow Your Body Down</td>
<td>Step-by-step instructions for various relaxation techniques (ie, deep breathing, guided imagery, progressive muscle relaxation)</td>
</tr>
<tr>
<td>Improve Your Thinking</td>
<td>Strategies to combat memory and thinking problems</td>
</tr>
<tr>
<td>Set Some Goals</td>
<td>Strategies to set realistic goals and carry out planned goals</td>
</tr>
<tr>
<td>Don’t Over Do It</td>
<td>Activity pacing strategies</td>
</tr>
<tr>
<td>Time for You</td>
<td>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</td>
</tr>
<tr>
<td>About Peripheral Neuropathy</td>
<td>Information about the symptoms of peripheral neuropathy, strategies to treat the symptoms of neuropathy, and safety precautions to take because of the symptoms of neuropathy</td>
</tr>
</tbody>
</table>

This table describes the content of the 10 modules embedded within the PROSPECT Web site.
The 7-point scale ranges from “very much worse” to “very much improved.” The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy Scale (QLQ-CIPN20) 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). The responses from each respective scale are then transformed and scored from 0 to 100, with higher scores representing worsening symptoms. The internal consistency reliability \( \alpha \) coefficient has been reported as .88, .88, and .78 for the sensory, motor, and autonomic subscales, respectively. Further evidence shows that the sensory and motor subscales are moderately-highly responsive to change (Cohen \( d = .82 \) and .48, respectively). Last, recent evidence supports the electronic administration of the QLQ-CIPN20 on the basis of high intraclass correlations (> .70) with paper/pencil administration. Last, we adapted questions from the Acceptability E-Scale to assess participant acceptability of and satisfaction with the PROSPECT Web site. The questionnaire contains 7 items that are scored on a 1 to 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 (ie, sex, age, race, ethnicity, employment status, marital status, education, and previous computer use) before the completion of the baseline assessments. Study staff abstracted participant cancer diagnosis (ie, disease and stage) and treatment (eg, chemotherapy type), medication dosage, and comorbid condition-related information from the patients’ electronic medical records.

**Study Procedures**

**Baseline**

After informed consent (eg, participants were informed of the nature of the PROSPECT and control groups), participants completed the baseline assessments (11-point worst and average CIPN pain NRS, PROMIS Pain Interference 4a, QLQ-CIPN20, demographic characteristics) via computer tablet. Participants were then notified of their study group assignment and e-mailed the 7-day worst pain diary. After completing the pain diary, the participants were e-mailed the PROSPECT Web site 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 4 and 8 Time Points**

Survey links to the same battery of assessments administered at baseline were e-mailed to participants 4 and 8 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 8 time point, participants in both groups completed the PGIC and individuals in the intervention group completed the Adapted Acceptability E-Scale and were contacted via telephone to discuss the most positive and negative aspects of PROSPECT. Participants were also e-mailed 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 e-mailed the link to the PROSPECT Web site.

**Statistical Analyses**

All data were analyzed using R version 3.4.0. Descriptive statistics of the centrality and dispersion of all survey data and demographic data were calculated. All analyses were calculated on the basis of the total number of individuals who completed the baseline and week 8 outcome measures. A power analysis was not conducted because of the pilot nature of this work (eg, determine an effect size to conduct larger studies testing this intervention) and because there were no previous studies testing the PROSPECT intervention in individuals with painful CIPN on which to base an effect size estimate.

**Primary Outcome**

We averaged patient’s responses from the 7-day worst CIPN pain diary for the baseline and week 8 time points. Participants must have completed 5 of the 7 daily worst pain ratings at the baseline and week 8 time points to be included in the analysis. Week 8 mean scores in worst CIPN pain intensity (0–10 NRS diary) were compared between groups using analysis of covariance adjusting for baseline scores. The robustness of our findings was examined via a post hoc intent-to-treat analysis. Multiple imputation (50 imputations; 50 iterations) (MICE R Package) was used to handle missing data. The same regression analysis was then repeated using the pooled data from the multiply imputed data sets.

**Secondary Outcomes**

Week 8 mean scores in CIPN symptom severity (QLQ-CIPN20 sensory and motor subscales), average pain (average CIPN pain NRS), and pain interference (PROMIS Pain Interference 4a) were compared between groups using analysis of covariance adjusting for baseline. Fisher exact test was used to analyze proportional differences between those who experienced “improvement” (PGIC score \( \geq 5 \)) and “no improvement” (PGIC score \( \leq 4 \)) in the 2 study arms.

**Acceptability and Satisfaction**

Descriptive statistics for the items of the Adapted Acceptability E-Scale were calculated. We also summarized responses from the semistructured telephone interviews to determine the most positive and negative aspects of PROSPECT and the biggest barriers to accessing and using the PROSPECT strategies.
Results

Patients

Participant recruitment occurred from May 1, 2016 to October 4, 2016. A review of the study sites' electronic medical records revealed 393 potentially eligible participants (Fig 1). After telephone screening procedures, 311 patients were deemed ineligible on the basis of inclusion/exclusion criteria. Of these 311 excluded participants, 18 experienced CIPN-related numbness, tingling, and pain, but rated their worst pain severity as <4 of 10. Also, 22 participants were eligible, but either declined to participate or were not available to meet in person to provide informed consent. Sixty participants were randomized to the PROSPECT intervention (n = 30) or wait-list control (n = 30) groups. Patient follow-up occurred from May 23, 2016 to December 19, 2016. After randomization, 13 participants terminated the study early because of personal reasons (eg, 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, respectively. There were no adverse events due to study participation reported by participants.

Patient characteristics are described in Table 2. Individuals in the PROSPECT group had higher levels of fatigue and sleep-related impairment compared with individuals in the control group; otherwise, there were no differences. When comparing protocol completers versus noncompleters, noncompleters 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.

Primary Outcome

Individuals with chronic painful CIPN who received the 8-week PROSPECT intervention had a mean change score of −.94 (SD = 1.36, range = −3.29 to 1.29, 95% confidence interval [CI] = −1.6 to −.28), whereas individuals in the wait-list control group had a mean change score of 0 in worst pain intensity (SD = 1.31, range = −3.43 to 2.86, 95% CI = −.63 to .63; Table 3). The difference in worst CIPN pain intensity improvements between groups was significant (B = −.91, P = .046, 95% CI = −1.79 to −.02, d = .58, n = 38). Three participants receiving PROSPECT and 1

![Figure 1](https://example.com/fig1.png) Consolidated Standards of Reporting Trials flow diagram. This shows the flow of participants through the duration of the study.
participant receiving treatment as usual experienced a clinically significant (>30%) reduction in worst CIPN pain intensity immediately post-treatment (n = 38; Fig 2).19 Results of the post hoc intent-to-treat analysis (n = 60) indicated that the difference in worst pain intensity improvement between groups was not statistically significant (B = −.64; P = .09; 95% CI = −1.38 to .10; d = −.42).

Secondary Outcomes
There were no significant differences in mean change scores for average pain (P = .18, d = .42), pain interference (P = .98, d = .01), or nonpainful CIPN sensory (P = .41, d = .23) or motor symptoms (P = .95, d = .02; n = 42; Table 3). Trends in average pain and pain interference across time indicated that PROSPECT provided no clear benefit over usual care. However, trends in nonpainful CIPN symptoms suggested that individuals receiving PROSPECT were experiencing considerable improvements as the study progressed. There was also a greater number of individuals in the PROSPECT group reporting improved impression of change after the completion of the trial, but the difference between groups was not significant (P = .21, d = .48, n = 41; Table 3).

Acceptability and Satisfaction
Overall, acceptability and satisfaction with the study and PROSPECT Web site was moderate to high, with mean Adapted Acceptability E-Scale item scores ranging from 3.26 to 4.58 of 5 (n = 19; Table 4). Participants reported that ease of use, the ability to print off work sheets on the basis of 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 was not enough information and/or strategies to help manage the symptoms of nonpainful neuropathy (eg, numbness and tingling). Participants also cited lack of time and difficulty changing symptom management practices as barriers to implementing the strategies they learned. Last, participants thought that PROSPECT would have been more beneficial if it contained additional cognitive strategies related to pain management (ie, cognitive restructuring), 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.

PROSPECT Usage
In terms of intervention use, the mean number of minutes individuals in the intervention group spent using PROSPECT and other symptom management resources (eg, 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 in the control group spent using symptom management strategies (eg, ice therapy, massage, stretching, yoga, distraction, exercise) varied across the 8-week study period (Table 5). In terms of medication changes,
there were more individuals in the PROSPECT group that increased neuropathic pain medication frequency/dose and pain medication frequency/dose not indicated as a first-line treatment for painful CIPN and/or neuropathic pain ("other analgesics").11,24 but otherwise, there were no considerable differences in the number of participants changing medication frequency/dose between groups (Fig 3). To further explore how changes in pain medication frequency/dose may have affected worst CIPN pain intensity improvement in individuals receiving PROSPECT (within primary aim protocol completers; n = 38), we compared week 8 worst pain intensity mean scores (adjusting for baseline) between groups in 2 ways: 1) removing individuals in the PROSPECT arm who increased their use of first-line neuropathic pain medications, and 2) removing individuals in the PROSPECT arm who

<table>
<thead>
<tr>
<th>OUTCOMES*</th>
<th>INTERVENTION, MEAN (SD)</th>
<th>CONTROL, MEAN (SD)</th>
<th>CONTRAST BETWEEN GROUPS†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst pain (n = 38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.04 (1.24)</td>
<td>4.78 (1.78)</td>
<td>B = −.91, P = .046, 95% CI = −1.79 to .02, d = .58</td>
</tr>
<tr>
<td>Week 4 (n = 39)</td>
<td>5.42 (2.32)</td>
<td>5.60 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>4.10 (1.81)</td>
<td>4.78 (1.93)</td>
<td></td>
</tr>
<tr>
<td>Average pain (n = 42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.37 (1.89)</td>
<td>3.91 (2.52)</td>
<td>B = −.83, P = .18, 95% CI = −2.05 to .40, d = .42</td>
</tr>
<tr>
<td>Week 4 (n = 39)</td>
<td>4.37 (2.11)</td>
<td>5.25 (2.36)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>4.58 (1.87)</td>
<td>5.35 (1.99)</td>
<td></td>
</tr>
<tr>
<td>Pain interference (n = 42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>57.81 (8.16)</td>
<td>57.33 (7.07)</td>
<td>B = .05, P = .98, 95% CI = −4.36 to 4.46, d = .01</td>
</tr>
<tr>
<td>Week 4 (n = 39)</td>
<td>57.47 (8.49)</td>
<td>55.54 (5.90)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>56.72 (7.96)</td>
<td>56.43 (7.74)</td>
<td></td>
</tr>
<tr>
<td>CIPN sensory (n = 42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>49.34 (16.68)</td>
<td>45.99 (20.1)</td>
<td>B = −3.61, P = .41, 95% CI = −12.43 to 5.21, d = .23</td>
</tr>
<tr>
<td>Week 4 (n = 39)</td>
<td>44.80 (23.10)</td>
<td>41.67 (18.70)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>40.41 (18.66)</td>
<td>41.95 (17.37)</td>
<td></td>
</tr>
<tr>
<td>CIPN motor (n = 42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>34.21 (17.04)</td>
<td>25.83 (18.41)</td>
<td>B = −.23, P = .95, 95% CI = −8.27 to 7.80, d = .02</td>
</tr>
<tr>
<td>Week 4 (n = 39)</td>
<td>30.23 (23.59)</td>
<td>23.24 (13.57)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>26.91 (17.71)</td>
<td>22.75 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Impression of change (n = 41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Weeks (improved)</td>
<td>9/19 (47.3%)</td>
<td>6/22 (27.3%)</td>
<td>OR = 2.35, P = .21, 95% CI = .55 to 10.84, d = .48</td>
</tr>
<tr>
<td>8 Weeks (no change or worse)</td>
<td>10/19 (52.7%)</td>
<td>16/22 (72.7%)</td>
<td></td>
</tr>
</tbody>
</table>

This table describes changes in primary and secondary outcome improvement over time between treatment groups.

*Week 4 data are documented to provide information related to time to response.
†Difference in week 8 mean scores adjusted for baseline scores. Impression of change scores were only compared at the week 8 time point.

Figure 2. Percent decrease in worst pain intensity because of use of PROSPECT or treatment as usual (n = 38). This figure shows the percentage of participants reporting various reductions in worst pain intensity after completion of the study.
Table 4. Adapted Acceptability E-Scale Scores (n = 19)

<table>
<thead>
<tr>
<th>Acceptability and Satisfaction; Adapted Acceptability E-Scale</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How easy was it to access the Web site on your computer?</td>
<td>4.58</td>
<td>.84</td>
<td>2 to 5</td>
</tr>
<tr>
<td>2. How understandable was the content presented within the Web site?</td>
<td>4.58</td>
<td>.69</td>
<td>3 to 5</td>
</tr>
<tr>
<td>3. How much did you enjoy using the Web site?</td>
<td>3.26</td>
<td>1.05</td>
<td>1 to 5</td>
</tr>
<tr>
<td>4. How helpful was it to read and participate in the Web site activities to help manage your symptoms related to CIPN (pain, physical functioning, anxiety, sleep disturbance, etc)?</td>
<td>3.36</td>
<td>.96</td>
<td>1 to 5</td>
</tr>
<tr>
<td>5. Was the amount of time it took to complete the activities presented within the Web site acceptable?</td>
<td>4</td>
<td>1.11</td>
<td>1 to 5</td>
</tr>
<tr>
<td>6. Was the amount of time it took to complete the study questionnaires at the baseline, 4-week, and 8-week time points acceptable?</td>
<td>4.42</td>
<td>1.02</td>
<td>1 to 5</td>
</tr>
<tr>
<td>7. Overall, how would you rate your satisfaction with the Web site?</td>
<td>3.95</td>
<td>.71</td>
<td>3 to 5</td>
</tr>
</tbody>
</table>

This table describes the descriptive statistics (mean, SD, range) of the Adapted Acceptability E-Scale Items at Week 8.

Table 5. PROSPECT or Other Symptom Management Resource Use According to Week

<table>
<thead>
<tr>
<th>Week</th>
<th>PROSPECT Use*</th>
<th>Symptom Management Use (Intervention)*,†</th>
<th>Symptom Management Use (Control)*,†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25.4 (0–90) (n = 14)</td>
<td>67.3 (0–390) (n = 15)</td>
<td>15.1 (0–120) (n = 10)</td>
</tr>
<tr>
<td>2</td>
<td>12.1 (0–60) (n = 12)</td>
<td>63.8 (0–300) (n = 12)</td>
<td>2.5 (0–15) (n = 6)</td>
</tr>
<tr>
<td>3</td>
<td>10 (0–20) (n = 6)</td>
<td>60 (0–210) (n = 6)</td>
<td>25 (0–160) (n = 8)</td>
</tr>
<tr>
<td>4</td>
<td>17.1 (0–60) (n = 14)</td>
<td>19.2 (0–140) (n = 12)</td>
<td>27.9 (0–360) (n = 19)</td>
</tr>
<tr>
<td>5</td>
<td>5.5 (0–30) (n = 10)</td>
<td>23 (0–180) (n = 10)</td>
<td>9.2 (0–60) (n = 10)</td>
</tr>
<tr>
<td>6</td>
<td>16.4 (0–72) (n = 13)</td>
<td>49 (0–420) (n = 13)</td>
<td>2.7 (0–25) (n = 15)</td>
</tr>
<tr>
<td>7</td>
<td>7.5 (0–35) (n = 13)</td>
<td>26.7 (0–120) (n = 13)</td>
<td>8.1 (0–45) (n = 12)</td>
</tr>
<tr>
<td>8</td>
<td>8.6 (0–30) (n = 18)</td>
<td>6.7 (0–60) (n = 17)</td>
<td>32.1 (0–495) (n = 21)</td>
</tr>
</tbody>
</table>

This table describes the mean number of minutes individuals in the intervention or control arm spent using PROSPECT and/or other symptom management resources over time.

*Mean number of minutes (range).
†Symptom management use in the PROSPECT group refers to pain management strategies (eg, physical therapy, meditation, pool therapy, massage) used by participants in addition to the strategies embedded within the PROSPECT Web site, whereas symptom management use in the control group refers to strategies used by participants to manage pain during the study (eg, ice therapy, massage, stretching, yoga, distraction, exercise). Type of symptom management strategies used by participants in each treatment group varied according to individual.

Figure 3. PROSPECT versus control medication changes during study (n = 45). This figure shows the number of instances that individuals (protocol completers) increased and/or decreased pain, anxiety, or sleep medication dosages. On the basis of the clinical practice guideline for CIPN treatment recommendations, neuropathic pain medications included: duloxetine, gabapentin, pregabalin, and antidepressants. Other analgesics included: oxycodone, morphine, ibuprofen, and acetaminophen.
increased their use of “other analgesics.” Results from these analyses indicated that the effect of PROSPECT on worst pain intensity was still statistically significant when removing individuals from the PROSPECT arm who increased their use of neuropathic pain medications (B = −1.07, 95% CI = −1.97 to −.15, P = .02; n = 36) and when removing individuals from the PROSPECT group who increased their use of “other analgesics” (B = −1.10, 95% CI = −2.10 to −.10, P = .03; n = 33).

Discussion

This 8-week, randomized controlled pilot trial showed that a self-guided online cognitive behavioral pain management program—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, nonpainful CIPN symptoms, average pain, or global impression of change.

Individuals with chronic painful CIPN interacting with the 8-week PROSPECT intervention reported a mean decrease in worst pain intensity of .94. The mean decrease in pain intensity found in this study is comparable with the effect of duloxetine, the only pharmacological agent currently recommended for the treatment of chronic painful CIPN. The authors of a randomized, crossover, placebo-controlled study reported that use of duloxetine 60 mg/d resulted in a mean decrease of 1.06 in average pain intensity in individuals with chronic painful CIPN (P = .003, d = .513). On the contrary, PROSPECT had no effect on the secondary outcome of average pain intensity. The comparison between average pain mean change scores between studies is challenging because the authors of the duloxetine trial assessed average pain over the past 24 hours, not 7 days. Nevertheless, the reported effect sizes and mean decreases for the 2 studies’ primary outcomes were similar for PROSPECT and duloxetine.

Although our findings supported the efficacy of PROSPECT in improving worst CIPN pain intensity compared with individuals receiving treatment as usual, results from post hoc sensitivity analyses suggest that these findings should be interpreted with caution. Few participants experienced a clinically significant reduction in worst CIPN pain intensity after PROSPECT usage. Clinically significant improvements in pain intensity represent a 30% reduction in pain. The overall worst CIPN pain intensity mean change score for individuals receiving PROSPECT was −.94 and only 3 individuals reported a clinically significant reduction in pain. Further, results from a post hoc intent-to-treat analysis with the full sample (N = 60) revealed that the effect of PROSPECT on worst pain intensity was not statistically significant (P = .09). Finally, because of the dearth of high-quality trials testing interventions for the treatment of painful CIPN, it is possible that changes in neuropathic pain medications and “other analgesics” may produce an analgesic effect in individuals with chronic painful CIPN. Thus, changes in the frequency/dosage of neuropathic pain medications or “other analgesics” may partially explain the efficacy of PROSPECT on worst pain intensity. However, the results from sensitivity analyses revealed that the effect of PROSPECT on worst CIPN pain intensity remained statistically significant after removing individuals in the PROSPECT arm who increased their use of neuropathic pain medications and “other analgesics,” respectively.

There have been no published studies reporting the effects of cognitive-behavioral pain management for nonpainful CIPN symptoms. Although nonpainful CIPN symptoms such as numbness and tingling are a result of peripheral nervous system damage (eg, dorsal root ganglia of primary sensory neurons), nonpainful CIPN symptoms are still associated with changes in the central nervous system. For example, the authors of a recent study showed that increased CIPN symptoms 1 month after neurotoxic chemotherapy are associated with changes in perfusion in brain areas associated with nociceptive processing (eg, 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 nonpainful CIPN symptoms. The results of this current study support this conclusion because individuals receiving PROSPECT had greater improvements in nonpainful CIPN symptoms over the 8-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 (eg, cognitive-behavioral pain management) can also influence nonpainful CIPN symptoms.

There were also no significant differences in pain interference between groups. Although physical function and 7-day recall of worst pain intensity are moderately-strongly correlated (r = .65), self-guided cognitive-behavioral pain management interventions are most effective when targeting a specific primary outcome. Therefore, perhaps if the PROSPECT intervention was tailored to include more physical activity training and educational resources, it would have had a greater effect on pain interference.

On the basis of trends in PROSPECT usage and worst pain intensity improvement, the results suggest that participants interacted with the Web site 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 (eg, electronic tracking or use of strategies in day-to-day activities) and the response rate to the self-report measures was low. Significant predictors of self-management intervention usage include health care professional guidance/support, ample amount of time to use the intervention, and high satisfaction with intervention content. PROSPECT usage may be bolstered in future studies if: 1) participants have an opportunity to interact with a health care professional (eg, weekly video or telephone call with nurses) to discuss pain-related symptoms and strategy use, 2) participants have more time to interact with the strategies of PROSPECT (eg, longer duration, scheduled time to interact with modules), and 3) additional interactive features within PROSPECT are
designed (eg, achievement badges, message boards/support groups, visually appealing). Improving self-guided cognitive-behavioral pain management intervention usage 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. Although this study did not contain a placebo control, psychoeducational interventions are prone to nonspecific effects (eg, study staff-participant interaction, participant motivation for participation, lack of blinding, credibility of treatment) that may have accounted for the efficacy of the intervention. We attempted to improve the assay sensitivity of the trial, or the ability to distinguish an effective treatment from an ineffective treatment by implementing strategies such as: (1) baseline participant worst CIPN pain intensity of 4 of 10 or greater, participant pain duration of at least 3 months since completion of chemotherapy, (3) flexible intervention dosing, (4) standardized data collection procedures for both groups, and (5) <3 treatment arms. 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 8 time point. However, an alternate explanation for this finding is that control group participants were not blinded to the intervention they were receiving (eg, were informed that the alternative group received PROSPECT) and thus, knew they were not receiving the intervention (nonspecific effect). Additional strategies we could have implemented to minimize or control for nonspecific effects include using a structurally equivalent control group and administering manipulation checks to determine if participants were using the treatment as intended. 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 study. First, the dropout rate was approximately 22%. This dropout rate is consistent with other self-guided cognitive behavioral pain management intervention studies and the demographic characteristics of the completers and noncompleters were similar between groups. However, because of 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, we did not conduct a power analysis because of the pilot nature of this study. Nevertheless, it is highly unlikely that this study was adequately powered to detect differences primary or secondary outcomes between groups because of the small sample size and high dropout rate. Third, although worst pain intensity improved after 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, greater use of other symptom management resources by individuals in PROSPECT 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. Sixth, participants were not blinded to what treatment (PROSPECT or wait-list control) they were receiving and we did not assess for participants’ expectations of improvement on the basis of study group assignment at baseline. Last, individuals receiving PROSPECT had higher levels of baseline depression, anxiety, 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.

Overall, currently there is 1 recommended pharmacological agent and no nonpharmacological modalities recommended for the treatment of chronic painful CIPN. This pilot study provides preliminary evidence supporting the efficacy of a self-guided cognitive-behavioral pain management intervention for improving worst pain intensity in individuals with chronic painful CIPN. However, because of 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, multimodal treatment approaches for chronic pain are beneficial because they target underlying pain as well as pain-related physiological mechanisms.

References


---

Self-Guided Cognitive Behavioral Strategies for Neuropathy