Impact of Pain on Symptom Burden in Chemotherapy-Induced Peripheral Neurotoxicity

Fawaz Mayez Mahfouz, BAdvSc1; Tiffany Li, MBiostat1; Hannah C. Timmins, PhD1; Lisa G. Horvath, MBBS, PhD2,3,4; Michelle Harrison, MBBS2; Peter Grimison, MBBS, PhD2,3; Gavin Marx, MBBS5; David Goldstein, MBBS6,7; and Susanna B. Park, PhD1

ABSTRACT

Background: Chemotherapy-induced peripheral neurotoxicity (CIPN) affects the quality of life of cancer survivors. However, the impact of pain on symptom burden remains undefined. This study aimed to define differences in the clinical symptom profile of patients with painful and nonpainful CIPN.

Patients and Methods: A total of 579 participants (median age, 59 years [IQR, 19 years]; F=66%) were assessed cross-sectionally 6 months posttreatment. CIPN severity was graded using multiple methods, including patient-reported outcome measures, a clinically graded scale (NCI-CTCAE), and a neurologic examination score. Participants were classified into subgroups based on patient symptom report, with painful CIPN characterized by the presence of shooting/burning pain, and nonpainful CIPN characterized by the presence of numbness or tingling without shooting/burning pain. Behavioral changes were assessed via structured patient interview regarding symptom impact on sleep, exercise, and treatment-seeking.

Results: Among 579 participants, 24% (n=140) reported painful CIPN, 48% (n=280) reported nonpainful CIPN, and 28% (n=159) had no CIPN. Participants with painful CIPN demonstrated higher CIPN severity than those with nonpainful CIPN across multiple measures, including NCI-CTCAE, neurologic grading, and patient report (all \(P<.05\)). Participants with painful CIPN were more likely to report that their symptoms affected their ability to exercise (\(P=.007\)), produced sleep impairment, and increased treatment-seeking behavior due to their symptoms (both \(P<.001\)) compared with participants with nonpainful CIPN. Conclusions: Overall, participants with painful CIPN reported higher scores across all CIPN severity measures, including behavioral changes. This study underlines the need for accurate identification of different CIPN subgroups in hopes of informing better treatment and rehabilitation options for cancer survivors with painful CIPN.

Background

Chemotherapy-induced peripheral neurotoxicity (CIPN) is associated with treatment with neurotoxic chemotherapies, including platinum-based agents, taxanes, vinca-alkaloids, bortezomib, and thalidomide. Because there are no preventive or treatment measures for CIPN, symptoms may require chemotherapy dose modification, which could reduce effectiveness. Furthermore, CIPN symptoms affect the quality of life (QoL) of cancer survivors, often producing long-term disability, including an impact on fine motor skills, walking, and gait.

The core symptoms associated with CIPN are sensory disturbances, including numbness and tingling. Neurotic pain, often described as shooting or burning pain, is less common, with only 33% of patients with CIPN reporting burning pain, compared with 77% reporting severe numbness and tingling. This discrepancy occurs for multiple neurotoxic drugs, with patients treated with taxanes, bortezomib, and platinum-based agents all reporting more severe tingling and numbness compared with neuropathic pain.

However, our understanding of the impact of painful CIPN on patients treated with chemotherapy is inadequate. In limited previous studies, participants with painful CIPN reported worse health-related QoL than those with nonpainful CIPN. Furthermore, painful CIPN may be associated with comorbidities, including fatigue, anxiety, and sleep impairments. However, the assessment of neuropathic pain in the context of CIPN remains a challenge. There is a lack of validated diagnostic tools that address pain and its impacts separately from nonpainful CIPN symptoms. Multiple studies use the clinically graded NCI-CTCAE scale for the quantification of neuropathy severity, which does not include neuropathic pain. Further, few patient-reported outcome measures (PROMs) for CIPN evaluation focus on identifying pain and its impact. The aim of this study was to understand the differences in prevalence and symptom burden of painful versus nonpainful CIPN.

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Patients and Methods

Participants

Eligible participants were cancer survivors aged ≥18 years and were 3 to 12 months post treatment with neurotoxic chemotherapy (including taxanes, platinum-based agents, bortezomib, thalidomide, and vinca alkaloids). Participants were assessed cross-sectionally on a single occasion. Relevant clinical data were retrieved from medical records, including sex and age. This study was approved by Sydney Local Health District (Royal Prince Alfred Hospital [RPAH] zone) and South Eastern Sydney Local Health District Human Research Ethics Committees, and informed consent was obtained from each participant.

CIPN and Pain Assessment: PROMs

Assessment tools are briefly described in the following sections, with further details available in Appendix 1 in the supplementary materials (available online with this article).

The validated 20-item EORTC Quality of Life Questionnaire—Chemotherapy-Induced Peripheral Neuropathy (EORTC QLQ-CIPN20) was used to assess CIPN. The total score as well as individual item scores assessing the impact of CIPN symptoms on patient function were investigated.

The Pain Numeric Rating Scale (PNRS) was used to assess the intensity of nerve pain experienced by participants in the 24 hours prior to testing. A modified Douleur Neuropathique 4 (DN4) was used to report the most common descriptors of pain in participants who had neuropathic pain, including a comparison of pain descriptors reported across different chemotherapy types.

A semistructured qualitative interview was conducted to collect information about participant symptoms and their impact, similar to previously conducted interviews.

Clinical Neuropathy Assessment

Trained researchers undertook a comprehensive neuropathy assessment protocol to grade CIPN severity, including clinical neuropathy grading scales and functional assessments.

The NCI-CTCAE sensory neuropathy subscale version 4.0 and the Total Neuropathy Score—clinical version (TNSc; John Hopkins University) were undertaken. Nerve conduction studies (NCS) were undertaken in the lower-limb sural and tibial nerves as per previous studies.

Functional assessments on participants’ dominant hand assessed sensory perception via Von-Frey monofilaments and grating orientation task (GOT), as well as fine motor skills via the grooved pegboard task.

Participant Classification

Participants were classified based on CIPN symptoms reported in the PROM (EORTC QLQ-CIPN20) as in previous studies. Participants who did not report any painful or nonpainful CIPN symptoms were placed in the “no CIPN” group and were excluded from further analyses. From the remaining cohort, the presence of painful CIPN was characterized using either EORTC QLQ-CIPN20 items or PNRS score (detailed in Appendix 1).

Statistical Analyses

Data analysis was undertaken using SPSS Statistics, version 27 (IBM Corp). Data were assessed for normality using the Shapiro-Wilk test, and nonnormally distributed data (P<.05) were presented as median (IQR). Mann-Whitney U tests were used to explore differences between CIPN outcome measure scores, clinical characteristics, neurophysiological measurements, and treatment factors of painful and nonpainful CIPN cohorts. Chi-square tests were used to explore group differences between participants treated with taxane and platinum-based chemotherapy in the painful CIPN cohort and to investigate behavioral changes associated with CIPN subgroups. Statistical significance was considered when P<.05.

Results

Demographics and Clinical History

A total of 579 participants with a median age of 59 years (IQR, 19 years) were assessed cross-sectionally 6 months post neurotoxic chemotherapy treatment. In total, 66% of the cohort were female (n=384). The most common cancer types were breast (32%; n=184), gastrointestinal (28%; n=162), and gynecologic (18%; n=102). The most common chemotherapy types were taxanes (57%; n=329) and platinum-based (33%; n=194).

Overall, 28% (n=159) reported no CIPN, 24% (n=140) reported painful CIPN, and 48% (n=280) reported nonpainful CIPN. Participants not reporting CIPN at the time of assessment were excluded from the analysis (n=159). Of those with CIPN (n=420), females were more likely to report painful CIPN than males (P=.02). However, there were no differences in cancer type, cancer stage, or chemotherapy type between patients with painful versus nonpainful CIPN (all P>.05) (Table 1).

There were no demographic differences between both groups in terms of age and body mass index (both P>.05). However, participants reporting painful CIPN were significantly farther from treatment completion (6 [IQR, 5] months) than participants with nonpainful CIPN (4 [IQR, 3] months) (P=.02) (Table 1).

Neuropathy Profiles and Subgroups

Participants with painful CIPN had a greater symptom burden than those with nonpainful CIPN across multiple measures, including the clinically graded scale (NCI-CTCAE; P<.001) (Table 2) and the PROM (EORTC QLQ-CIPN20; P<.001) (Figure 1A and Table 2, and Supplementary...
Table 1. Clinical and Demographic Characteristics of Participants With CIPN

<table>
<thead>
<tr>
<th></th>
<th>Painful CIPN (n=140)</th>
<th>Nonpainful CIPN (n=280)</th>
<th>Total (n=420)</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>Clinical characteristics</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Sex</td>
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<td>Female</td>
<td>105 (75)</td>
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<td>Male</td>
<td>35 (25)</td>
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<td>Diabetes</td>
<td>13 (9)</td>
<td>34 (12)</td>
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<tr>
<td>Cancer type</td>
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<tr>
<td>Breast</td>
<td>49 (35)</td>
<td>80 (29)</td>
<td>129 (31)</td>
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<td>Gynecologic (cervical, endometrial, and ovarian)</td>
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<td>43 (15)</td>
<td>72 (17)</td>
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<td>20 (7)</td>
<td>30 (7)</td>
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<td>Gastrointestinal/ Colorectal and pancreatic</td>
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<td>106 (38)</td>
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<td>21 (7)</td>
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<td>Other</td>
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<td>15 (4)</td>
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<td>143 (51)</td>
<td>228 (54)</td>
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<tr>
<td>Platinum-based</td>
<td>45 (32)</td>
<td>114 (41)</td>
<td>159 (38)</td>
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<td>Bortezomib</td>
<td>4 (3)</td>
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<td>Cancer stage</td>
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<td>3 (1)</td>
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<td>I</td>
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<td>39 (9)</td>
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<td>III</td>
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<tr>
<td>IV</td>
<td>26 (19)</td>
<td>75 (27)</td>
<td>101 (24)</td>
<td></td>
</tr>
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<td>30 (7)</td>
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<td>9 (2)</td>
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<td>No</td>
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<td>206 (74)</td>
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<td>55 (20)</td>
<td>75 (18)</td>
<td></td>
</tr>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
<td>.90</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>61.0 (18.0)</td>
<td>60.0 (18.0)</td>
<td>60.5 (18.0)</td>
<td></td>
</tr>
<tr>
<td>BMI, median (IQR), kg/m²</td>
<td>26.9 (6.1)</td>
<td>26.3 (6.4)</td>
<td>26.7 (7.0)</td>
<td>.40</td>
</tr>
<tr>
<td>Months since treatment completion, median (IQR)</td>
<td>6.0 (5.0)</td>
<td>4.0 (3.0)</td>
<td>4.0 (4.0)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Comparisons between both groups were performed using chi-square tests. Demographic characteristics were compared using Mann-Whitney U tests. Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neurotoxicity.

*Bold indicates statistically significant P value (P<.05).

Table S1). Participants with painful CIPN also had worse neurologic examination scores (TNSc; P<.001) (Figure 1B), including higher report of sensory (P=.003) and motor (P=.001) symptoms in the extremities (Table 2). However, there were no significant differences in pinprick or vibration scores, functional assessments (all P>.05), or sural (P=.10) or tibial amplitudes (P=.30) between the groups (Table 2).

Items assessing the impact of symptoms on function on the PROM (EORTC QLQ-CIPN20) were investigated. Participants with painful CIPN reported significantly more functional impairments across all of these items compared with participants with nonpainful CIPN (all P<.003) (Figure 2).

The severity of neuropathic pain was reported by participants with painful CIPN on the PNRS, focused on...
the shorter recall period of 24 hours. The median PNRS score was 4 (IQR, 6) out of 10, with 31% (n=44) reporting no pain in the 24 hours prior to testing (score, 0/10). Overall, the level of neuropathic pain on PNRS was significantly correlated with CIPN severity across all measures (all \( P < .05 \)), including the PROM (Figure 3A), the neurologic examination score (Figure 3B), and the clinically graded scale (\( r = 0.3; \ P = .002 \)).

### Table 2. Comparison of Neuropathy Outcomes Between Participants With Painful and Nonpainful CIPN

<table>
<thead>
<tr>
<th>Assessment Tools</th>
<th>Painful CIPN (n=140)</th>
<th>Nonpainful CIPN (n=280)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically graded scale (NCI-CTCAE)</td>
<td>2.0 (1.0)</td>
<td>1.0 (1.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PROM (EORTC QLQ-CIPN20)</td>
<td>22.8 (19.0)</td>
<td>12.3 (12.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neurologic examination score (TNSc)</td>
<td>5.0 (4.0)</td>
<td>4.0 (3.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TNS: sensation</td>
<td>1.0 (1.0)</td>
<td>1.0 (1.0)</td>
<td>.003</td>
</tr>
<tr>
<td>TNS: weakness</td>
<td>0 (1.0)</td>
<td>0 (0)</td>
<td>.001</td>
</tr>
<tr>
<td>Sensory and functional assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average pegboard time, s</td>
<td>77.9 (25.6)</td>
<td>73.9 (25.4)</td>
<td>.40</td>
</tr>
<tr>
<td>GOT threshold, mm</td>
<td>3.7 (2.6)</td>
<td>3.8 (2.6)</td>
<td>.80</td>
</tr>
<tr>
<td>Two-point discrimination distance</td>
<td>15.0 (6.0)</td>
<td>13.0 (6.0)</td>
<td>.09</td>
</tr>
<tr>
<td>TNS: pinprick</td>
<td>1.0 (2.0)</td>
<td>1.0 (1.0)</td>
<td>.20</td>
</tr>
<tr>
<td>TNS: vibration</td>
<td>0 (1.0)</td>
<td>0 (1.0)</td>
<td>.30</td>
</tr>
<tr>
<td>Tibial amplitudes, mV</td>
<td>8.9 (5.8)</td>
<td>9.3 (6.7)</td>
<td>.30</td>
</tr>
<tr>
<td>Sural amplitudes, ( \mu )V</td>
<td>6.0 (6.9)</td>
<td>7.3 (7.8)</td>
<td>.10</td>
</tr>
</tbody>
</table>

Mann-Whitney \( U \) tests were used to explore differences between CIPN outcome measure scores, sensory and functional assessments, and neurophysiological measurements of painful and nonpainful CIPN cohorts. Higher scores on CIPN outcome measures and sensory and functional assessments, as well as lower amplitudes of neurophysiological measures, indicate worse impairment. Abbreviations: CIPN, chemotherapy-induced peripheral neurotoxicity; EORTC QLQ-CIPN20, EORTC Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy; GOT, grating orientation task; PROM, patient-reported outcome measure; TNS, Total Neuropathy Score; TNSc, Total Neuropathy Score–clinical version.

*Bold indicates statistically significant \( P \) value (\( P < .05 \)).

Similarly, those who reported more severe pain in the past week (EORTC QLQ-CIPN20) had worse CIPN severity across all measures compared with those reporting lower pain severity (all \( P < .05 \)). Common descriptors of pain are reported in Appendix 2 in the supplementary materials.

### Subgroups Within Moderate-to-Severe CIPN Cohort

To examine further subgroup differences, comparisons were made between participants with moderate-to-severe CIPN symptoms with pain (n=102) and without pain (n=121). Even within the moderate-to-severe CIPN cohort, those with painful CIPN symptoms had worse impairments across all CIPN severity measures, including the PROM, the clinically graded scale, and the neurologic examination score (all \( P < .05 \)) (Table 3). However, there were no demographic, neurophysiological, or functional differences between the groups (\( P > .05 \)) (Table 3).

### Comparison of CIPN Subgroups Among Different Chemotherapy Types

The 2 largest chemotherapy-type cohorts (paclitaxel and oxaliplatin) were selected for group comparisons. There were significant differences in the prevalence of pain between the paclitaxel and oxaliplatin chemotherapy cohorts (28% vs 39%, respectively; \( P = .03 \)) (Supplementary Figure S1). Group comparisons between paclitaxel-treated...
and oxaliplatin-treated participants can be found in Appendix 2 and Supplementary Tables S2 and S3.

Impact of Painful CIPN on Sleep, Exercise, and Treatment-Seeking Behavior

To characterize the impact of painful CIPN on behavior and patient function, we compared the painful (n = 87) and nonpainful CIPN (n = 193) cohorts who completed the structured interview in terms of self-reported sleep dysfunction, exercise impairment, and treatment-seeking behavior.

Participants with painful CIPN were more likely to report that their symptoms affected their ability to exercise (odds ratio [OR], 2.1; P = .007) than those without pain, with 43% (n = 37) in the painful CIPN cohort reporting their exercise ability being affected by CIPN compared with 26% (n = 51) of those without pain. Similarly, participants with painful CIPN were more likely to report that they had trouble sleeping (OR, 2.8; P < .001), with 47% (n = 41) in the painful CIPN cohort reporting sleep dysfunction due to CIPN compared with 24% (n = 46) of those without pain (Supplementary Table S4).

In addition, participants with painful CIPN were more likely to report seeking treatment of their symptoms than those without pain (OR, 3.2; P < .001) (Supplementary Table S4), with 69% (n = 60) of the painful CIPN cohort reporting trying to find treatment options compared with 41% (n = 79) of those with nonpainful CIPN. Furthermore, participants with painful CIPN were 4 times as likely to report the use of medication to ameliorate neuropathy than those with nonpainful CIPN (P < .001; Supplementary Table S5). These medications included anticonvulsants (pregabalin and gabapentin) and antidepressants (duloxetine and amitriptyline). In total, 12% (n = 17) of the painful CIPN cohort were receiving medication for CIPN at the time of assessment, compared with 3% (n = 9) of the nonpainful CIPN cohort.

Discussion

This study investigated neuropathic pain and its impact on symptom severity, sensory function, and behavior in participants with CIPN. Overall, 33% of participants with

Abbreviations: CIPN, chemotherapy-induced peripheral neurotoxicity; EORTC QLQ-CIPN20, EORTC Quality of Life Questionnaire—Chemotherapy-Induced Peripheral Neuropathy; Q, question; TNSc, Total Neuropathy Score—clinical version.
CIPN reported painful CIPN, which was associated with higher symptom severity across all CIPN outcome measures. The participants with painful CIPN reported more functional consequences than those without pain and were more likely to take neuropathy medications and report sleep dysfunction and exercise intolerance. Pain descriptors were similar between paclitaxel-treated and oxaliplatin-treated cohorts; however, pain was more prevalent in the oxaliplatin-treated cohort.

Other cohort studies have reported a similar prevalence of neuropathic pain, ranging between 20% and 33% of patients, in line with our results. In this study, participants with painful CIPN had worse global CIPN severity across all measures compared with participants with nonpainful CIPN. The presence of painful CIPN was associated with worse impairment of activities of daily living, a particularly reduced ability to distinguish temperature, more instability when standing or walking, and difficulty writing and manipulating small objects with fingers.

However, there were no group differences in performance on functional assessments and NCS. This suggests a potential separation between the perception of overall symptom burden and objective measures of neuropathy severity. Discrepancies between patient-reported symptoms of CIPN and neurologic examination have been previously identified, suggesting that these assessment tools address different aspects of CIPN. Patient reports of CIPN symptom severity and impact often provide a broader perspective compared with focal quantification of neurologic status. In addition, most neurophysiological measures of CIPN, including NCS, measure large nerve fiber function, whereas small nerve fiber dysfunction is less accessible to measure, presenting a potential limitation in fully capturing objective deficits. Importantly, patient report remains a key metric of CIPN severity, particularly given the lack of efficacy of measures such as NCS to identify differences between CIPN cohorts.

Participants with painful CIPN may be higher symptom reporters due to their increased symptom severity. A

### Table 3. Comparison Between Participants With Worse CIPN (NCI-CTCAE ≥ 2) and No Pain Versus With Pain

<table>
<thead>
<tr>
<th>Assessment Tools (NCI-CTCAE Cutoff ≥2)</th>
<th>Moderate-to-Severe CIPN Without Pain (n=121) Median (IQR)</th>
<th>Moderate-to-Severe CIPN With Pain (n=102) Median (IQR)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPN outcome measures</td>
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<tr>
<td>Clinically graded scale (NCI-CTCAE)</td>
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<td>2 (0)</td>
<td>.009</td>
</tr>
<tr>
<td>PROM (EORTC QLQ-CIPN20)</td>
<td>17.5 (12.0)</td>
<td>27.9 (18.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neurologic examination score (TNSc)</td>
<td>5.0 (5.0)</td>
<td>6.0 (5.0)</td>
<td>.01</td>
</tr>
<tr>
<td>TNS: sensation</td>
<td>2.0 (1.0)</td>
<td>2.0 (1.0)</td>
<td>.50</td>
</tr>
<tr>
<td>TNS: weakness</td>
<td>0 (1.0)</td>
<td>0 (1.0)</td>
<td>.006</td>
</tr>
<tr>
<td>Sensory and functional assessments</td>
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<tr>
<td>Average pegboard time, s</td>
<td>81.0 (30.2)</td>
<td>79.7 (27.3)</td>
<td>.50</td>
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<tr>
<td>GOT threshold, mm</td>
<td>4.8 (3.5)</td>
<td>3.8 (3.0)</td>
<td>.10</td>
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<tr>
<td>Two-point discrimination distance</td>
<td>15.0 (5.0)</td>
<td>16.0 (5.0)</td>
<td>.40</td>
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<tr>
<td>TNS: pinprick</td>
<td>1.0 (2.0)</td>
<td>1.0 (1.0)</td>
<td>.20</td>
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<td>TNS: vibration</td>
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<td>0 (2.0)</td>
<td>.90</td>
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<tr>
<td>Demographic characteristics</td>
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<td>Age, y</td>
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<td>BMI, kg/m²</td>
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<td>27.2 (7.9)</td>
<td>.70</td>
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<tr>
<td>Neurophysiological measures</td>
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<tr>
<td>Tibial amplitudes, mV</td>
<td>8.9 (6.5)</td>
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<td>.70</td>
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<td>Sural amplitudes, µV</td>
<td>6.0 (7.1)</td>
<td>5.0 (7.0)</td>
<td>.20</td>
</tr>
</tbody>
</table>

Mann-Whitney U tests were used to explore differences between CIPN outcome measure scores, sensory and functional assessments, clinical characteristics, and neurophysiological measurements of painful and nonpainful CIPN cohorts. Higher scores on CIPN outcome measures and sensory and functional assessments, as well as lower amplitudes of neurophysiological measures, indicate worse impairment. Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neurotoxicity; EORTC QLQ-CIPN20, EORTC Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy; GOT, grating orientation task; PROM, patient-reported outcome measure; TNS, Total Neuropathy Score; TNSc, Total Neuropathy Score–clinical version.
*Bold indicates statistically significant P value (P < .05).
previous study found that participants who reported painful CIPN also reported higher anxiety and depression, suggesting that there may be a modulating effect of psychological factors on pain perception in patients with CIPN. However, the direction of this association remains uncertain, given that patients with painful CIPN were more likely to have persisting anxiety and depression following treatment, in contrast to patients with nonpainful CIPN, who demonstrated greater improvements in anxiety and depression following treatment cessation.

The presence of neuropathic symptoms, including pain, negatively impacts the QoL of cancer survivors. In this study, the presence of painful CIPN affected patient-reported sleep, exercise, treatment-seeking behavior, and functional capacity. Although one previous study also highlighted the association between painful CIPN and comorbidities, including increased sleep dysfunction, fatigue, anxiety, and depression, research on the comorbidities associated with painful CIPN remains limited and represents a gap in enabling personalized management strategies for people with CIPN.

This study also found that oxaliplatin-treated patients had overall worse CIPN symptoms, significantly lower rural amplitudes, and greater functional changes in sensory perception and fine motor skills than those treated with paclitaxel. The different CIPN profiles of taxane and platinum-based chemotherapies have been previously reported, with reports at 1-year follow-up being similar to the current study. On the contrary, there were no differences in subjective or objective measures of CIPN between taxane-treated or platinum-treated patients at 5-year follow-up. With regard to pain, in this current study it was significantly more prevalent in oxaliplatin-treated patients than paclitaxel-treated patients. Interestingly, oxaliplatin-treated patients with painful CIPN also benefitted the most from duloxetine treatment in clinical trials, suggesting that different pain phenotypes may guide treatment responsiveness between chemotherapy types. Understanding differences in the chemotherapy-specific profiles of CIPN is important to guide patients and clinicians in understanding the likelihood of symptom recovery and adaptation over time.

To date, treatment options recommended for the management of painful CIPN remain limited. In this study, only 12% of participants with painful CIPN reported taking anticonvulsants or antidepressants for neuropathy treatment. This reflects similar experiences with low medication uptake in Australian and international settings. Although duloxetine is recommended for the treatment of painful CIPN by international guidelines, in real-world practice, duloxetine treatment of painful CIPN is limited, with high rates of nonresponse and side effects leading to lack of tolerability. Better phenotyping of patients to determine who is most responsive to duloxetine and other therapies will likely improve real-world outcomes.

Although there are emerging strategies for the management of neuropathic pain, including both pharmacologic and nonpharmacologic approaches, both will require the identification of patient subgroups likely to benefit most. Novel therapies, such as targeted drug delivery and neurostimulation methods, hold promise for reducing neuropathic pain but require additional testing and validation. Preliminary findings suggest that nonpharmacologic approaches, such as cognitive behavioral therapy, might improve QoL in patients with neuropathic pain and be more acceptable to patients.

Overall, this study provides a clearer understanding of differing symptom patterns in a large cohort. We used a combination of subjective and objective measures of CIPN as well as the combination of patient-reported and clinically graded outcome measures of CIPN. An issue limiting the previous understanding of painful CIPN is the use of combined descriptors of CIPN, collapsing sensory and painful symptoms of CIPN into a singular measure. For this reason, we used specific PROM items that assessed numbness, tingling, and shooting or burning pain in the last 7 days to capture a broader recall period and separate patients into groups according to neuropathic pain. However, these measures are not specifically validated to identify neuropathic pain. Although we did use validated neuropathic pain tools to assess pain intensity and descriptors, we did not use them for the purpose of participant classification due to the recall period only pertaining to the last 24 hours prior to participant testing.

Given that prior studies have demonstrated a “coasting” effect for up to 3 months post treatment completion, we chose to examine a cross-sectional cohort between 3 and 12 months post treatment completion. However, the cross-sectional nature of this study may be a limitation, and future prospective analyses will provide insights into the development of painful CIPN over time. Furthermore, we included multiple cancer and chemotherapy types in the analysis and did not control for all preexisting conditions that cause peripheral neuropathy or pain. However, >70% of this cohort developed neuropathy during treatment, suggesting that the CIPN symptoms identified were related to treatment-emergent toxicity rather than other factors. Furthermore, the inclusion criteria were deliberately broad to capture a naturalistic cohort reflecting patients receiving chemotherapy in a clinical setting. Although participants were asked about functional limitations, this study did not quantify the number of falls or participant balance performance. In addition, participants did not report whether they had tried medications to treat neuropathic symptoms previously and why these were discontinued.

Overall, given the outcomes of this study, we recommend that neuropathic pain be assessed in research and
clinical settings as part of a comprehensive CIPN assess-
ment. The tools used for this purpose should use a recall
period longer than 24 hours, such as the EORTC QLQ-
CIPN20. Other CIPN outcome measures, including the
clinically graded scale (NCI-CTCAE) and the neurologic ex-
amination score (TNSc), which are used to assess CIPN
severity, do not include questions to address neuropathic
pain severity, and additional tools are required to address
this. Finally, we recommend assessment of the impact of
neuropathic pain on patient function and behavior, be-
cause our study has highlighted the long-term and delete-
rious consequences of pain on cancer survivors with CIPN.

Current guidelines for CIPN discuss the assessment
of CIPN and include potential treatment options.40,45
However, these guidelines lack information relevant to
patient subgrouping and phenotyping, particularly pa-
ients with neuropathic pain. The use of PROMs remains
important in identifying clinically relevant symptom pat-
terns, whereas NCS may not provide useful information in
the classification of CIPN subgroups. Critically, the lack of
accurate assessment of painful and nonpainful CIPN
symptoms in clinical trials may lead to inaccurate results
regarding intervention efficacy. Accordingly, it is essential
that appropriate outcome measures be used to enable dif-
ferentiation of painful and nonpainful symptoms.

Conclusions

Although the pathophysiological mechanisms underly-
ing the differences in symptom expression within CIPN
remains unclear, improved screening for pain and
associated functional changes will allow a better appre-
ciation of symptom burden and encourage more tai-
lored intervention strategies to improve the QoL of
cancer survivors.

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