Electronic versus paper-pencil methods for assessing chemotherapy-induced peripheral neuropathy

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Knoerl R, Gray E, Stricker C, Mitchell SA, Kippe K, Smith G, Dudley WN, Lavoie Smith EM. Electronic versus paper-pencil methods for assessing chemotherapy-induced peripheral neuropathy. Support Care Cancer. 2017 Nov;25(11):3437-3446. doi: 10.1007/s00520-017-3764-y. Epub 2017 Jun 2. PubMed PMID: 28577231.

Abstract:

Purpose: The aim of this study is to examine and compare with the validated, paper/pencil European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy Scale (QLQ-CIPN20), the psychometric properties of three electronically administered patient reported outcome (PRO) measures of chemotherapy-induced peripheral neuropathy (CIPN): (1) the two neuropathy items from the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), (2) the QLQ-CIPN20, and (3) the 0–10 Neuropathy Screening Question (NSQ). **Methods:** We employed a descriptive, cross-sectional design and recruited 25 women with breast cancer who were receiving neurotoxic chemotherapy at an academic hospital. Participants completed the paper/pencil QLQ-CIPN20 and electronic versions of the QLQ-CIPN20, PRO-CTCAE, and NSQ. Internal consistency reliability, intraclass correlation, and concurrent and discriminant validity analyses were conducted. **Results:** The alpha coefficients for the electronic QLQ-CIPN20 sensory and motor subscales were 0.76 and 0.75. Comparison of the electronic and paper/pencil QLQ-CIPN20 subscales supported mode equivalence (intraclass correlation range >0.91). Participants who reported the presence of numbness/tingling via the single-item NSQ reported higher mean QLQ-CIPN20 sensory subscale scores ($p < 0.001$). PRO-CTCAE neuropathy severity and interference items correlated well with the QLQ-CIPN20 electronic and paper/pencil sensory ($r = 0.76$; $r = 0.70$) and motor ($r = 0.55$; $r = 0.62$) subscales, and with the NSQ ($r = 0.72$; $r = 0.44$). **Conclusion:** These data support the validity of the electronically administered PRO-CTCAE neuropathy items, NSQ, and QLQ-CIPN20 for neuropathy screening in clinical practice. The electronic and paper/pencil versions of the QLQ-CIPN can be used interchangeably based on evidence of mode equivalence.

Keywords: Psychometrics | Chemotherapy-induced peripheral neuropathy | Peripheral nervous system disease/chemically induced | Patient-reported outcomes

Article:

Chemotherapy-induced peripheral neuropathy (CIPN) occurs in up to 64% of individuals receiving neurotoxic chemotherapy (e.g., platinums and taxanes) for the treatment of oncological and hematological malignancies [1, 2, 3, 4, 5, 6]. Individuals experience a variety of symptoms such as numbness, tingling, and burning in the extremities that persist for months to years after the completion of neurotoxic anti-cancer therapy [7, 8]. These symptoms may negatively affect physical function and quality of life and may necessitate chemotherapy dose reductions or discontinuation. These changes in therapy can compromise treatment efficacy and increase the risk of mortality [5, 9, 10].

Currently, several patient- and provider-related barriers hinder CIPN assessment in clinical practice. First, patients often do not accurately report their symptoms due to difficulty describing their symptoms (e.g., numbness and tingling) [11, 12]. Patients may also be reluctant to report CIPN symptoms for fear that doing so may lead to dose reductions or treatment discontinuation [13]. Further, clinicians often lack the time and expertise necessary to complete comprehensive neuropathy examinations (e.g., reflex, vibration, and strength assessments) [11, 14, 15] and there are currently few well-validated neuropathy self-report screening instruments for use in clinical practice.

Another barrier to CIPN assessment in clinical practice is that there is no “gold standard” measure. While a few psychometrically sound self-report CIPN measures are available, complex scoring and administration complicate their use in clinical practice [16, 17]. For example, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy Scale (QLQ-CIPN20) patient reported outcome (PRO) measure has been extensively used to evaluate CIPN severity in the USA and Europe [18]. The QLQ-CIPN20’s psychometric properties have been evaluated [18, 19], but its administration (paper/pencil) and scoring may be too cumbersome to make it feasible for use in busy clinical settings.

Another measure commonly used by clinicians to grade CIPN severity is the peripheral neuropathy items of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [20]. However, the measurement properties (e.g., reliability, validity, and responsiveness) of those items may be suboptimal [17, 19, 21, 22]. Moreover, provider-reported CTCAE grades for neuropathy do not correlate strongly with patient-reported CIPN severity [23]. Recent evidence suggests that, compared to clinician reporting alone, adding patient reporting of cancer treatment-related symptoms may provide a more reliable and valid measurement of symptom severity [21, 24, 25]. In addition, measures that quantify the patient’s perspective may encourage the discussion of symptoms between patients and clinicians [26]. To encourage patient reporting, the National Cancer Institute initiated development of the Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE™) [27, 28], which has since demonstrated generally favorable measurement properties in evaluations using both quantitative and qualitative techniques [27, 28, 29]. While this measure, which has two items addressing

CIPN, holds promise for improving CIPN measurement, the PRO-CTCAE neuropathy items have not been evaluated in comparison to well-validated CIPN measures.

One way to facilitate efficient CIPN assessment in clinical settings is through the use of technology that allows patients to self-report their CIPN symptoms using brief, validated measures administered electronically. The use of such technology may alert clinicians to the presence of CIPN symptoms and lead to the prioritization of CIPN assessment. However, the psychometric properties of electronic versions of PRO CIPN measures have not yet been tested. Thus, the primary purpose of this study was to compare to the well-validated, paper/pencil QLQ-CIPN20 the psychometric properties of electronic versions of three patient-reported CIPN outcome measures: (1) the two PRO-CTCAE numbness and tingling severity and interference items, (2) the QLQ-CIPN20, and (3) the 0–10 Neuropathy Screening Question (NSQ). The secondary aims were to examine the mode equivalence of the paper/pencil and electronic versions of the QLQ-CIPN20, and to evaluate the concurrent validity of the psychometric properties of the PRO-CTCAE neuropathy items with the clinician-reported CTCAE.

Methods

Design, sample, and setting

This study employed a descriptive, cross-sectional design. Convenience sampling was used to recruit 25 individuals with breast cancer receiving neurotoxic chemotherapy from a comprehensive cancer center. To be eligible, participants had to be 18 years or older with a diagnosis of breast cancer, English-speaking and -reading, capable of using a computer, and receiving neurotoxic chemotherapy. Each participant signed informed consent before participation. The study was approved by the IRB at the University of Michigan.

Measures

EORTC QLQ-CIPN20. This 20-item self-report measure quantifies sensory (e.g., numbness/tingling), motor (e.g., problems with ambulation due to numbness/tingling), and autonomic (e.g., dizziness) CIPN symptoms and associated functional limitations. The recall period is the past 7 days. Items are scored using a one to four scale, with one representing “not at all” and four representing “very much” [18]. Each subscale is linearly transformed from a 0 (no neuropathy) to 100 (severe neuropathy) point scale [30]. The internal consistency reliability alpha coefficients for the sensory, motor, and autonomic subscales has been reported as 0.88, 0.88, and 0.78, respectively [19]. The sensory and motor subscales are moderately to highly responsive to change (d = 0.82 and 0.48) [19]. The capacity of the QLQ-CIPN20 to distinguish those who did and did not receive neurotoxic chemotherapy confirms its discriminant validity [19].

CTCAE—sensory neuropathy grading criteria. Neuropathy was also evaluated by study providers using the CTCAE (version 4.0) [20]. The CTCAE grading criteria for sensory neuropathy are based on the evaluation of objective and subjective parameters (e.g., reflexes, tingling, alterations in activities of daily living). Toxicity is graded from 1 to 5; higher grades represent worse sensory neuropathy (1 = asymptomatic and/or loss of deep tendon reflexes; 5 =

death). The scale is subject to floor effects, and has been shown to lack sensitivity to detect small changes in neuropathy due to its broad scoring categories (e.g., diminished reflexes and paresthesias are grouped into one category) [17, 19, 22]. The scale also has low inter-rater reliability and low concurrent validity when compared to patient-reported measures of neuropathy with strong measurement properties [16, 17, 19]. Despite its limitations, the CTCAE was used in this study because it is currently the standard measure used in most oncology clinical trials and we were interested in assessing its performance when compared to the PRO-CTCAE.

PRO-CTCAE—numbness/tingling severity and interference items. The PRO-CTCAE item library contains 124 items reflecting 78 symptomatic cancer treatment-related symptomatic toxicities. The recall period is the past 7 days. Items are scored from zero to four, and higher scores represent greater symptom severity and interference [27, 28]. Previous studies have supported the content validity, concurrent validity, responsiveness of change, and test-retest reliability of the PRO-CTCAE item library [27, 29]. For this study, we evaluated the two PRO-CTCAE items addressing CIPN, which ask patients to rate the severity of the numbness and tingling in their hands or feet (severity item) at its worst in the past 7 days, and how much these symptoms have interfered with usual or daily activities (interference item). The CIPN numbness/tingling severity and interference items have demonstrated moderate test-retest reliability as evidenced by intraclass correlation coefficients (ICCs) of 0.80 and 0.55, respectively. Also, the PRO-CTCAE numbness/tingling severity ($r = 0.32$) and interference items ($r = 0.34$) have exhibited low-moderate correlations with the EORTC QLQ-C30 [27], demonstrating moderate reliability and validity in comparison to measures of quality of life. However, these items have not yet been compared to validated CIPN measures.

NSQ. The NSQ is an electronic CIPN screening item that was created specifically for use within the Carevive® Cancer Care Planning System. Patients first indicate (yes/no) if they have experienced numbness and tingling in their hands or feet in the past 7 days. If they respond yes, patients then rate the severity of the numbness and tingling in their hands or feet using a zero to ten (worse symptom severity) numerical rating scale. The NSQ's psychometric properties have not been previously evaluated.

Procedures

Participants reported their CIPN symptoms using a web-based cancer care planning system (Carevive®) that was designed to facilitate the collection of patient- and provider-reported data (e.g., medical/cancer history and patient-reported outcomes) and to generate a customized patient care plan comprised of CIPN treatment recommendations. A previous study has shown that the Carevive® Care Planning system possesses a high degree of patient-related feasibility, usability, acceptability, and satisfaction [31]. Patients interacted with the computerized care planning system using a tablet computer (screen size = 9.4 × 6.6 in) while waiting for their scheduled outpatient provider visit. At the patient's third and final study visit, and after becoming comfortable using the tablet to report their cancer symptoms, the patients completed the electronic versions of the QLQ-CIPN20, NSQ, and PRO-CTCAE. These measures were embedded within the computerized care planning system. In the exam room, advanced practice providers graded their patients' CIPN severity using a paper/pencil version of the CTCAE. After

the provider left the room, trained study personnel administered the paper/pencil version of the QLQ-CIPN20.

Statistical analysis

All data analysis procedures were conducted using Statistical Package for the Social Sciences version 23.0, and R 3.3.0. The analytic approaches used to test internal consistency reliability, concurrent validity, discriminant validity, and mode equivalence are described below.

Reliability

The internal consistency reliability of the QLQ-CIPN20's sensory and motor subscales (paper/pencil and electronic versions) was evaluated using Cronbach's alpha. Pearson's correlation was calculated for the two-item autonomic scale (paper/pencil and electronic versions) because Cronbach's alpha is a poor measure of internal consistency when the scale contains less than 3–4 items [32]. A Cronbach's alpha coefficient ≥0.8 was expected for each subscale.

Concurrent validity

Using multiple Pearson correlations, the concurrent validity of the QLQ-CIPN20, PRO-CTCAE, and NSQ was evaluated. Pearson correlations were calculated to evaluate the associations among the paper/pencil QLQ-CIPN20, electronic PRO-CTCAE, and NSQ; among the electronic QLQ-CIPN20, PRO-CTCAE, and NSQ; and between the electronic PRO-CTCAE numbness/tingling severity and interference items and clinician-reported CTCAE grade for sensory neuropathy.

Discriminant validity

The discriminant validity of the NSQ was evaluated using independent-sample *t* tests to examine differences in QLQ-CIPN20 subscales scores between patients who did and did not report neuropathy symptoms. We hypothesized that those who reported numbness and tingling via the NSQ would have significantly higher mean scores on the sensory subscale of the QLQ-CIPN20 than those who did not. We did not expect to find significant differences on the motor and autonomic subscales of the QLQ-CIPN20 because those scales do not contain questions pertaining to numbness and tingling. Additionally, sensitivity and specificity analyses were conducted to investigate the NSQ's accuracy as a screening measure, as compared to the QLQ-CIPN20 sensory subscale.

Mode equivalence

Mode equivalence between the paper/pencil and electronic QLQ-CIPN20 subscales (i.e., sensory, motor, autonomic) and individual items were evaluated by assessing (1) the magnitude of the difference in mean subscale scores between modes and (2) the level of between-mode agreement. The magnitude of the differences between mean scores was evaluated by determining standardized effects sizes (Cohen's *d*). Cohen's *d* was obtained by dividing the mean difference by the pooled standard deviation [34]. Differences in mean subscale and item scores between the

two modes were assessed using paired *t* tests. An effect size of 0.20 is considered a small effect size and values below this benchmark were interpreted as supporting the comparability of responses collected using different modes of administration [33, 34]. Mode equivalence was further evaluated using ICC using the ICC (3.1), in the notation of Shrout and Fleiss [35], in a two-way analysis of variance model. An ICC of >0.7 was expected for each comparison between the paper/pencil and electronic subscales [36].

Results

Sample characteristics

Stage IV breast cancer, as defined by the American Joint Committee on Cancer [37], was the most common cancer diagnosis (36%); the remainder of the participants had non-metastatic breast cancer. Most participants had previously undergone surgery (64%) or radiation therapy (48%) for cancer treatment. Almost all participants were receiving neurotoxic chemotherapy: paclitaxel (72%) or docetaxel (24%). Based on the cumulative dose of paclitaxel or docetaxel received, 63% of these participants fell in the moderate CIPN risk category [38, 39, 40, 41]. Eighty percent of the participants were white, 88% had completed some college education, and 100% had previously used a computer before beginning the study (Table 1). Twenty three of the participants completed all the required surveys; however, one of the 23 did not report scores for the autonomic scale of the paper/pencil version of the QLQ-CIPN20 ($n = 22$).

Table 1. Baseline characteristics of enrolled patients ($N = 25$)

Variable	Frequency (%)
Gender	
Female	25 (100)
Race	
American Indian or Alaska native	1 (4)
Asian	2 (8)
Black or African American	2 (8)
White	20 (80)
Ethnicity	
Hispanic or Latino	1 (4)
Not Hispanic or Latino	24 (96)
Education	
High school or less	3 (12)
Some college	7 (28)
Undergraduate degree	10 (40)
Graduate degree	5 (20)
Employment status	
Employed	12 (48)
Retired	6 (24)
Homemaker	2 (8)
Disabled	5 (20)
Marital status	
Married or partnered	19 (76)
Single	2 (8)
Divorced	4 (16)

Variable	Frequency (%)
Cancer stage[a]	
Stage I	3 (12)
Stage II	6 (24)
Stage III	7 (28)
Stage IV	9 (36)
Hormone receptor status	
Positive	18 (72)
Negative	7 (28)
Her2/neu status	
Positive	12 (48)
Negative	13 (52)
Surgery	
No surgery	9 (36)
Lumpectomy	7 (28)
Mastectomy	9 (36)
Chemotherapy type	
Paclitaxel	18 (72)
Docetaxel	6 (24)
Carboplatin[b]	1 (4)
Cumulative M^2 dose category: Paclitaxel (n = 18)[c]	
Low risk: 0–700	3 (16.7)
Moderate risk: 700–1400	9 (50)
High risk: >1400	6 (33.3)
Cumulative M^2 dose category: Docetaxel (n = 6)[d]	
Low risk: 0–300	0
Moderate risk: 300–600	6 (100)
High risk: > 600	0
Radiation therapy status	
Planned, not started	8 (32)
Complete	4 (16)
Not planned or receiving	13 (52)

This table describes the demographic characteristics of the recruited sample at baseline

[a]Cancer stage was determined based on the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual* (7th Edition) [37]

[b]No data available to guide cumulative dose category

[c]Cumulative M^2 dose ranges for paclitaxel-induced neuropathy risk were generated based upon dose-related neurotoxicity patterns described in the literature [40, 41]

[d]Cumulative M^2 dose ranges for docetaxel-induced neuropathy risk were generated based upon dose-related neurotoxicity patterns described in the literature [42, 43]

Descriptive statistics for the QLQ-CIPN20, CTCAE, PRO-CTCAE, and NSQ are provided in Table 2. Patients' mean scores on the sensory, motor, and autonomic subscales of the electronic and paper/pencil QLQ-CIPN20 were similar. The mean score on the CTCAE was 1.0 (SD = 0), while the mean scores on the PRO-CTCAE numbness/tingling severity and interference items were 0.83 (SD = 0.83, range = 0–2) and 0.44 (SD = 0.66, range = 0–2). The percentage of participants reporting "0" scores, the lowest possible score for the PRO-CTCAE numbness/tingling severity and interference items, were 43.48 and 65.22%, respectively. All participants were given CTCAE grades of 1, the lowest possible score. Score comparisons

between the CTCAE and PRO-CTCAE for each patient are illustrated in Fig. 1. Lastly, the mean score on the NSQ was 1.91 (*SD* = 2.31, range = 0–7).

Table 2. QLQ-CIPN20, CTCAE, and NSQ sample statistics (*N* = 23)

Scale	Mean	Median	Standard deviation	Range	Proportion at floor	Proportion at ceiling
QLQ-CIPN20						
Paper/pencil sensory subscale	11.43	7.41	11.33	0–44	21.8	0
Electronic sensory subscale	12.72	7.02	11.97	0–44	13.0	0
Paper/pencil motor subscale	7.75	4.17	10.33	0–38.08	47.8	0
Electronic motor subscale	8.33	4.17	11.10	0–37.5	43.5	0
Paper/pencil autonomic subscale (*n* = 22)	6.82	0.0	11.10	0–33.33	68.2	0
Electronic autonomic subscale	7.25	0.0	11.04	0–33.33	65.2	0
CTCAE						
CTCAE grade	1.0	1.0	0	1	100	0
PRO-CTCAE—Numbness/tingling item	0.83	1.0	0.83	0–2	43.5	0
PRO-CTCAE—interference item	0.44	0.0	0.66	0–2	65.2	0
NSQ						
NSQ	1.91	1.0	2.31	0–7	47.8	0

This table describes descriptive statistics (mean, median, SD, range, % at floor, % at ceiling for the QLQ-CIPN20 subscales, CTCAE, and PRO-CTCAE CIPN items, and NSQ

For all scales, higher scores represent greater CIPN symptom severity (e.g., increased numbness and tingling) and/or associated functional impairment due to CIPN symptoms

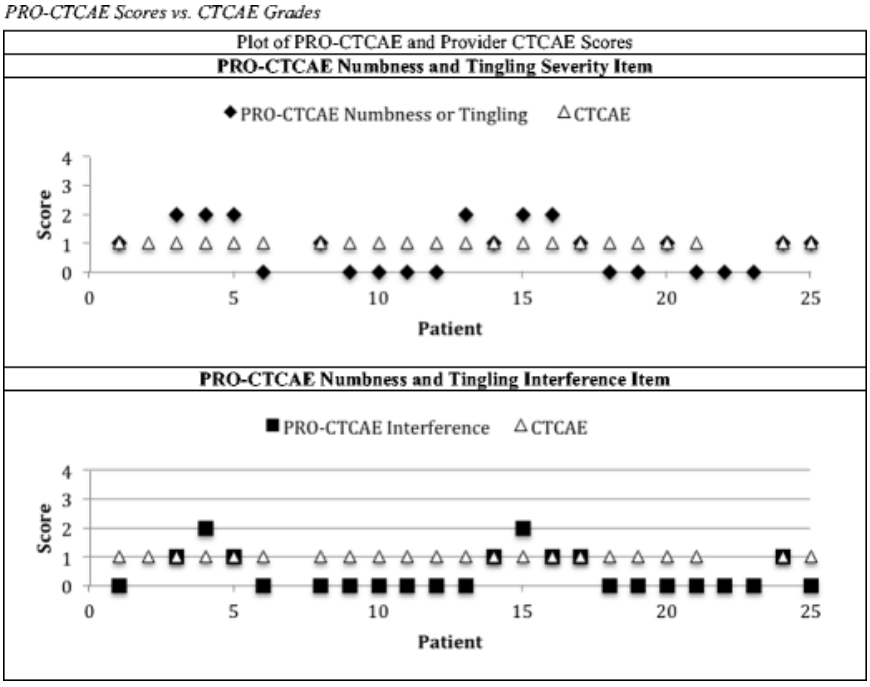

Figure 1. PRO-CTCAE Scores vs. CTCAE Grades. This figure illustrates the differences in PRO-CTCAE numbness and tingling severity and interference item scores compared to provider-reported CTCAE sensory neuropathy grades for each patient enrolled in the study. Note: case 7 was missing CTCAE grade and PRO-CTCAE scores. CTCAE scores appear to be higher than PRO-CTCAE item scores because the CTCAE is scored from 1 to 5 (1 = minimal neuropathy symptoms), whereas the PRO-CTCAE items are scored from 0 to 4 (0 = no neuropathy)

Reliability

Cronbach's alphas for the sensory and motor subscales of the electronic QLQ-CIPN20 were 0.76 and 0.75, and the two items of the autonomic scale were not correlated with one another ($r = -0.02$, $p > 0.05$). The Cronbach's alpha of the paper/pencil QLQ-CIPN20 sensory and motor subscales were 0.79 and 0.75. The two items of the paper/pencil autonomic scale were also not correlated ($r = 0.02$).

Concurrent validity

The sensory and motor subscales of the paper/pencil and electronic QLQ-CIPN20 were significantly correlated to both PRO-CTCAE items. The NSQ was significantly correlated with the sensory subscale of the paper/pencil ($r = 0.66$) and electronic ($r = 0.67$) QLQ-CIPN20 and with both PRO-CTCAE items (severity $r = 0.72$; interference $r = 0.44$) (Table 3). Further, since all patients were graded by clinicians as having CTCAE grade 1 sensory neuropathy, the planned evaluation of the associations between CTCAE grades and PRO-CTCAE scores could not be pursued.

Table 3. QLQ-CIPN20, NSQ, and PRO-CTCAE correlations ($N = 23$)

Scale		**Electronic QLQ-CIPN20**			**Paper/Pencil QLQ-CIPN20**			**PRO-CTCAE numbness and tingling**		**NSQ**
	Subscale	Sensory	Motor	Autonomic	Sensory	Motor	Autonomic ($n = 22$)	Severity	Interference	
PRO-CTCAE numbness and tingling	Severity	0.76[a]	0.55[b]	0.14	0.70[a]	0.62	0.09	1		
	Interference	0.78[a]	0.77[a]	0.28	0.72[a]	0.80[a]	0.21	0.72[a]	1	
NSQ		0.69[a]	0.26	−0.09	0.66[a]	0.28	−0.16	0.72[a]	0.44[b]	1

This table describes correlations between mean paper/pencil and electronic QLQ-CIPN20, PRO-CTCAE, and NSQ mean scores.
No adjustments for multiple comparisons were made
[a]Correlation significant at the 0.01 level (two-tailed)
[b]Correlation significant at the 0.05 level (two-tailed)

Discriminant validity

Twelve participants who reported experiencing numbness/tingling via the NSQ (score ≥1) also reported significantly higher mean scores for the electronic QLQ-CIPN20 sensory subscale (Yes: $M = 21.3$, $SD = 10.6$; No: $M = 3.4$, $SD = 2.6$), $t(12.43) = -5.67$ ($p < 0.001$) and the paper/pencil sensory scale (Yes: $M = 19.1$, $SD = 10.6$; No: $M = 3.0$, $SD = 3.2$), $t(13.21) = -5.02$ ($p < 0.001$) than those who did not. Thus, this item demonstrated acceptable discriminant validity. As expected, significant differences between those who did/did not report numbness/tingling on the NSQ were not observed among the motor and autonomic subscales of the electronic and paper/pencil QLQ-CIPN20.

Using the QLQ-CIPN20 sensory subscale, the NSQ had a sensitivity of 0.67 ($CI = 0.41, 0.87$) and specificity of 1.0 ($CI = 0.36, 1.0$). Sensitivity and specificity testing for the motor and

autonomic subscales was not warranted as there were no significant differences between the motor and autonomic QLQ-CIPN20 subscales when we compared those who did/did not report numbness/tingling on the NSQ.

Table 4. Standardized effect sizes for QLQ-CIPN20 scale comparisons

QLQ-CIPN20 subscale or item	Standardized effect size paper/pencil vs. electronic	Confidence interval
Subscale		
Sensory subscale	0.11	−0.07, 0.29
Motor subscale	0.05	−0.1, 0.21
Autonomic subscale	No variance[a]	NA
Individual items		
Sensory subscale		
Tingling in hands	0.16	−0.02, 0.34
Tingling in toes	0.0	−0.15, 0.15
Numbness in hands	0.13	−0.19, 0.45
Numbness in toes	0.06	−0.22, 0.34
Pain in hands	0.0	−0.36, 0.36
Pain in toes	0.0	−0.51, 0.51
Walking problems	0.09	−0.21, 0.38
Difficulty distinguishing hot/cold	No variance[a]	NA
Hearing problems	0.08	−0.08, 0.24
Motor subscale		
Cramps in hands	0.19	−0.07, 0.44
Cramps in feet	0.15	−0.06, 0.36
Trouble holding pencil/writing	0.0	−0.28, 0.28
Trouble grasping small objects	0.14	−0.05, 0.33
Trouble opening jars	0.0	−0.15, 0.15
Problems walking due to foot drop	No variance[a]	NA
Trouble walking upstairs	0.02	−0.40, 0.44
Trouble driving/feeling pedals in car	−0.53[b]	−1.12, 0.07
Autonomic subscale		
Dizziness	0.0	NA
Blurred vision	No variance[a]	NA

This table describes standardized effect sizes for the difference between paper/pencil and electronic QLQ-CIPN20 mean scores (per subscale and item)

[a]No variance indicates that scores between measures were identical and thus an effect size of the difference could not be computed

[b]Effect size estimate may have been influenced by the presence of three outliers

Mode equivalence

Tables 4 and 5 describe the results of the mode equivalence analysis. The effect sizes (using Cohen's *d*) of the mean differences for the sensory and motor subscales were 0.11 (*CI* = −0.7, 0.29) and 0.05 (*CI* = −0.1, 0.21), respectively. At the item level, a majority (18/19) of the QLQ-CIPN20 items had effect sizes smaller than 0.20 when the mean differences between modes were examined. For the autonomic subscale, an effect size could not be calculated because there was no variance in the responses. The mode equivalence ICC for the sensory, motor, and autonomic subscales comparing the paper/pencil and electronic QLQ-CIPN20 were 0.91, 0.93, and 1.0,

respectively. Lastly, 14/19 items of the QLQ-CIPN20 demonstrated high levels of between-mode agreement (ICC > 0.70).

Table 5. Intraclass correlation coefficients for agreement between paper/pencil and electronic QLQ-CIPN20 scores

QLQ-CIPN20 scales/items	ICC for electronic vs. paper/pencil
Subscale	
Sensory subscale	0.91
Motor subscale	0.93
Autonomic subscale	1.0
Individual items	
Sensory subscale	
Tingling in hands	0.90
Tingling in toes	0.93
Numbness in hands	0.70
Numbness in toes	0.78
Pain in hands	0.63
Pain in toes	0.24
Walking problems	0.74
Difficulty distinguishing hot/cold	1.0
Hearing problems	0.93
Motor subscale	
Cramps in hands	0.81
Cramps in feet	0.87
Trouble holding pencil/writing	0.78
Trouble grasping small objects	0.89
Trouble opening jars	0.94
Problems walking due to foot drop (motor 6)	1.0
Trouble walking upstairs	0.48
Trouble driving/feeling pedals in car	[a]
Autonomic subscale	
Dizziness	1.0
Blurred vision	1.0

This table describes intraclass coefficients for the agreement between the paper/pencil and electronic QLQ-CIPN20 subscales and items

[a]The ICC could not be calculated as the variance for the electronic administration of the QLQ-CIPN20 was zero

Discussion

The trivial effect sizes of the mean between-mode pairwise differences for the extensively validated paper/pencil subscales of the QLQ-CIPN20 [2, 18, 19] and the electronic version subscales provide support for use of the electronic QLQ-CIPN20 and for the use of pooled data from both modes of administration in analysis. In this study, the paper/pencil version of the QLQ-CIPN20 demonstrated lower ratings of internal consistency reliability than it has in other research [18, 19]: a previous study in a sample (n = 376) with prominent score variability demonstrated internal consistency reliability coefficients of 0.88, 0.88, and 0.78 for the sensory, motor, and autonomic subscales of the paper/pencil QLQ-CIPN20, respectively [19]. Given that the recommended minimum sample size recommended to calculate Cronbach's alpha is approximately 300 participants, or 10 participants per item [42], the lower internal consistency

reliability coefficients we found may be artifacts of our small sample (n = 23) and/or the low variability in responses.

Our data demonstrate a lack of CTCAE score variability, consistent with other published reports showing that the provider-reported CTCAE neuropathy grades lack some sensitivity, may be subject to floor effects, and may not adequately distinguish subtle differences in neuropathy severity [17, 19, 21, 22]. Based on our and other investigator's findings, the PRO-CTCAE may be a more precise and responsive measure of neuropathy severity than provider-reported CTCAE grades. Ideally, our observations should be replicated and extended in a larger and more diverse sample. Future studies should also examine responsiveness to change.

The use of electronic PRO CIPN measures for the assessment of CIPN has important implications for practice. Utilizing PRO CIPN measures may simplify collecting neuropathy symptom data in the clinical setting because the measure can be administered in the waiting room (via tablet) or at the patients' home (via patient portal) before the patients' clinic visits. Previous research has demonstrated that an oncology care planning program that incorporated PRO CIPN measures had high ratings of patient-related feasibility, usability, acceptability, and satisfaction [43]. Additionally, brief and psychometrically sound electronic PRO CIPN measures may increase the feasibility of collecting neuropathy severity data in the clinical setting. For example, the one-item NSQ demonstrated strong concurrent validity when compared to the longer and more complex QLQ-CIPN20, which is clinically relevant because brief measures are more feasible for use in clinical practice than multi-item measures. In busy practice settings, a single-item screening measure could quickly alert providers that more comprehensive neuropathy examinations (e.g., reflexes/vibration) are warranted to assess the need for prompt treatment or chemotherapy dose modification to prevent severe and protracted CIPN. Lastly, the use of PRO CIPN measures may increase the efficiency, completeness, and accuracy of neuropathy data capture since patients will be directly reporting their CIPN symptoms into the electronic database (minimizing data entry errors) and allowing for completion of PRO measures between clinic visits.

Limitations

Several caveats should be considered in interpreting these study findings. First, the analysis was conducted using a small sample and in a homogeneous patient population (females with breast cancer who experienced low CIPN symptom severity while receiving neurotoxic chemotherapy). Thus, the results are preliminary and cannot be generalized to other populations (e.g., males, patients with other cancers and/or severe neuropathy). Further, in comparing modes, our study design did not control for order or memory effects when the participants completed the electronic and paper/pencil QLQ-CIPN20. Also, the mode equivalence analyses were underpowered, so our findings require replication in larger samples. The instruments were also administered at one time point, so we were unable to assess responsiveness to change in CIPN severity over time or determine the test-retest reliability of the measures.

In conclusion, since CIPN is currently an underreported symptom of cancer treatment, valid and brief instruments are needed to strengthen the assessment of CIPN in clinical practice. This study provides preliminary evidence supporting the validity of the electronic PRO-CTCAE, QLQ-

CIPN20, and NSQ for the assessment of CIPN. However, due to the small sample of this study and the limited psychometric testing that was conducted, future studies are needed to more fully characterize the properties of these measures in diverse samples. Further testing may include the examination of the concurrent validity, responsiveness to change, and minimal clinically important difference of these electronic measures (i.e., electronic QLQ-CIPN20, PRO-CTCAE, and NSQ). With further psychometric testing, these electronic CIPN PRO measures may be integrated into clinical practice to facilitate the assessment of CIPN-related symptoms.

Acknowledgements

We would like to acknowledge the Carevive Systems, Inc. for allowing us to test these instruments within their computerized care planning system. In addition, we would like to acknowledge Jill Hayden, RN, and Shraddha Pardesi, MS, BPharm for their assistance with patient accrual; James P. Kelly, IV, BS, Deborah Lee, MSN, FNP, ACNP-BC, and Grace Kanzawa, BSN, RN for their assistance with data collection; Megan Williams, PA-C, Anne Clotfelter, MS, NP-C, Tamara Ghormley, MS, NP-C, and Joan Armstrong, MS, NP-C for participating in the study as the clinical providers; Kelly Scheu, MS, NP-C, for her assistance with facilitating use of the technology within the clinical practice setting; and Celia Bridges, BA, BSN for her assistance with editing the final manuscript.

Compliance with ethical standards

Source of funding: Dr. Carrie Stricker is the CCO of Carevive® Systems Inc., which provided the Care Planning System used in this study without cost. Dr. Stricker reports grants from Genentech, Inc., personal fees from Carevive Systems, Inc., during the conduct of the study; personal fees from Carevive Systems, Inc. and other from Carevive Systems, Inc., outside the submitted work; . Mr. Evan Gray reports personal fees from Centerpoint Human Services, personal fees from Cardinal Innovations Healthcare, personal fees from Piedmont Research Strategies, Inc., outside the submitted work. Dr. Ellen Smith reports receiving a grant from Genentech Inc., during the conduct of the study; personal fees from American Society of Clinical Oncology, grants from National Institute of Health, outside the submitted work. Dr. William Dudley reports personal fees from Piedmont Research Strategies, Inc., during the conduct of the study; personal fees from Piedmont Research Strategies, Inc., outside the submitted work.

This study was conducted with oversight from the University of Michigan IRBMED: HUM00084475 Written informed consent was obtained from all enrolled participants.

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