Journal of Pediatric Oncology Nursing
1–11

DOI: 10.1177/1043454220980253
journals.sagepub.com/home/jpo
SAGE

Assessment of Pediatric Chemotherapy-Induced Peripheral Neuropathy Using a New Patient-Reported Outcome Measure: The P-CIN

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Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is commonly experienced by children receiving neurotoxic chemotherapy. No validated pediatric CIPN patient-reported outcome (PRO) measures exist. **Purpose:** To test sensitivity, internal consistency reliability, content and convergent validity, and feasibility of the Pediatric Chemotherapy-Induced Neuropathy (P-CIN), an electronic PRO measure for assessing CIPN in children who received neurotoxic chemotherapy. **Method:** Five experts evaluated content validity of the 14-item P-CIN. Children 5 to 17 years old with CIPN ($N = 79$) completed the P-CIN via tablet computer; a subset ($n = 26$) also underwent neurological examinations using the Pediatric–Modified Total Neuropathy Score. Following preliminary analyses, one item was deleted and three others modified. The revised P-CIN was retested with patients ($n = 6$) who also completed the Bruininks–Oseretsky Test of Motor Proficiency motor function assessment. Means, item response ranges, standard deviations, content validity indexes, Cronbach's alphas, and correlation coefficients were calculated. **Results:** Mean participant age was 11.25 ($SD = 4.0$) years. Most had acute leukemia (62.5%) and received vincristine (98.7%). Content validity index coefficients ranged from .80 to 1.0 ($p = .05$). For 9 of 14 items, responses ranged from 0 to 4 or 5; response ranges for toe numbness, pick up a coin, and three of four pain items were 0 to 3. After deleting one item, Cronbach's alpha coefficient was .83. P-CIN scores were strongly associated with Pediatric-Modified Total Neuropathy Score ($r = .52$, $p < .01$) and Bruininks–Oseretsky Test of Motor Proficiency ($r = -.83$, $p = .04$) scores. Sixty-eight percent of children 6 to 17 years old completed P-CIN independently. **Discussion:** Preliminary evidence suggests that the 13-item P-CIN is internally consistent, is valid, and can be completed independently by children ≥ 6 years. However, we recommend additional testing.

Keywords

chemotherapy-induced peripheral neuropathy, pediatric, side effects of treatment, psychometrics

Introduction

Advances in chemotherapy treatment have contributed to high cure rates and prolonged survival among children with cancer (American Cancer Society, 2020). Despite these beneficial therapeutic effects, chemotherapy causes many disabling side effects that can last for years after cancer treatments have ended (Kandula et al., 2018; Purser et al., 2014).

Empirical evidence suggests that nearly all pediatric patients who receive neurotoxic chemotherapy (e.g., taxanes, platinum compounds, vinca alkaloids) experience chemotherapy-induced peripheral neuropathy (CIPN; Gilchrist et al., 2017; Kandula et al., 2016; Lavoie Smith

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et al., 2015). Peripheral neuropathy may manifest as a variety of sensory, motor, and autonomic signs and/or symptoms. Sensory CIPN symptoms include upper and lower extremity numbness, tingling, neuropathic pain, and reduced sensation in response to mechanical and temperature stimuli. Patients with CIPN may also exhibit motor signs and symptoms including weakness, cramps, and reduced or absent deep tendon reflexes. Less commonly, autonomic symptoms, such as vincristine-induced constipation and hoarseness, can also affect children with CIPN (Kandula et al., 2016; Lavoie Smith et al., 2013; Lavoie Smith et al., 2015).

In addition to CIPN symptoms, children often experience functional deficits such as difficulty zipping or buttoning clothing, and grasping and holding objects like toys, eating utensils, and writing implements (Kandula et al., 2016). Neuropathy-related balance abnormalities due to lower extremity weakness, foot drop, sensory deficits in the plantar surfaces of the feet, and decreased ankle strength and range of motion can lead to inactivity and falls (Khan et al., 2014; Lehtinen et al., 2002; Ness et al., 2013; Varedi et al., 2017; Wright et al., 1998), and can persist for months to years following the cancer diagnosis (Gilchrist et al., 2017; Gilchrist & Tanner, 2018; Ness et al., 2012; Ness et al., 2013; Wright et al., 1998). In a large cohort study of 415 survivors (ages 30-40 years and $>$10 years from diagnosis) who had received vincristine treatment as children, approximately 40% had impaired reflexes, 33% severely weak ankle dorsiflexion, 30% weak ankle plantar flexion, 30% weak knee extension, and 15% impaired balance (Ness et al., 2012). Most concerning is that 46.5% of these young survivors experienced impaired walking ability that was significantly worse than adults aged 60 and older.

Currently, no known treatments can effectively prevent or minimize CIPN in children. The most common approach for managing CIPN is to reduce, delay, or discontinue neurotoxic drug treatment. However, chemotherapy dose reduction is not an optimal CIPN management approach because cancer survival rates may be compromised. Clinical trials testing new CIPN interventions are desperately needed, but such studies are difficult to conduct with children, mainly due to the current lack of a noninvasive, age-appropriate, and psychometrically strong pediatric CIPN patient-reported outcome (PRO) measure that can be used to quantify intervention efficacy.

The published literature (Kandula et al., 2016; Mohrmann et al., 2017; Mora et al., 2016; Smolik et al., 2018) provides evidence that pediatric CIPN measurement is challenging, and that no validated CIPN PRO measures have been designed to overcome the assessment challenges. CIPN assessment is particularly difficult when evaluating children $<$ 5 years of age (Lavoie Smith et al., 2013). Most published measurement studies conducted with children have tested complex objective measurement approaches using one of several Total Neuropathy Score© (TNS©) variants (Smith et al., 2020). The composite measure TNS was initially tested in adults (Smith et al., 2008). Several pediatric versions have subsequently been tested, for example, the Pediatric-Modified TNS (ped-mTNS©; Gilchrist et al., 2009; Gilchrist et al., 2014; Gilchrist & Tanner, 2013, 2018) and the Total Neuropathy Score–Pediatric Vincristine (Lavoie Smith et al., 2013). Researchers have also validated an abbreviated two-item TNS variant, the V-Rex, which assesses only vibration sensibility and deep tendon reflexes (Lavoie Smith et al., 2013). Each variant provides a grading rubric and a summed score for various combinations of the following items: sensory, motor, and autonomic neuropathy symptoms; pin prick, light touch, and vibration sensibility; strength; and deep tendon reflexes.

Although pediatric TNS variants have demonstrated strong psychometric properties (Gilchrist & Tanner, 2013; Griffith et al., 2010; Kandula et al., 2016), these measures are not always feasible for routine use in clinical or research settings. Factors that limit common TNS use are (1) the need for TNS-trained assessors, (2) the time and clinical space needed to conduct the assessments, (3) occasional discomfort associated with some of the testing procedures (e.g., pin prick), and (4) some children's limited ability to focus and cooperate during a lengthy TNS-based examination.

In contrast, a pediatric CIPN PRO measure has the potential to overcome some of the measurement barriers associated with the TNS testing procedures (e.g., training requirements, discomfort). Furthermore, PRO measures eliminate the need for assessor training and may provide a more accurate and patient-centric assessment of CIPN than do the commonly used clinician-graded scales, which often underestimate neuropathy severity (Gilchrist et al., 2014; Gilchrist & Tanner, 2013; Lavoie Smith et al., 2013).

The absence but potential utility of a validated CIPN PRO measure led the authors to develop a new pediatric PRO measure: the Pediatric Chemotherapy-Induced Neuropathy (P-CIN). The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy 20-item subscale (Postma et al., 2005)—a CIPN PRO measure used to assess CIPN in adults—served as a model when developing the P-CIN's unique items. To address known challenges of pediatric PRO CIPN assessment, the measure uses age-appropriate language and graphics to help children describe their sensations of numbness, tingling, and neuropathic pain. The P-CIN incorporates fun, engaging tasks to assess CIPN-associated fine and gross motor functional limitations (e.g.,

picking up coins, hopping on one foot, walking on heels). Finally, the P-CIN is designed for administration using a tablet computer, which is entertaining for children and efficient in providing clinicians and researchers with electronic data.

The purpose of this study was to test the psychometric properties (i.e., sensitivity, internal consistency reliability, content and convergent validity, and clinical feasibility) of the P-CIN for assessing CIPN in children who had received or were receiving neurotoxic chemotherapy.

Method

Study Design and Aims

Using a prospective, cross-sectional design, we tested several of the P-CIN's psychometric properties. The study's specific aims were to evaluate P-CIN (1) sensitivity, (2) internal consistency reliability, (3) content and convergent validity, and (4) clinical feasibility.

Sample and Setting

We recruited children 5 to 17 years old ($N = 79$) from two academic sites: the University of Michigan Comprehensive Cancer Center/C. S. Mott Children's Hospital and Children's Minnesota Cancer and Blood Disorders Program. Each site's institutional review board approved the study.

Eligible participants were children 5 to 17 years of age who (1) had received or were currently receiving neurotoxic chemotherapy drugs (e.g., vinca alkaloids, platinums, taxanes, thalidomide, bortezomib), (2) had reported peripheral neuropathy, (3) could use a tablet computer, (4) were willing and able to follow the survey instructions, and (5) could speak and understand English. Children were ineligible if they (1) and their parent(s) could not read English, (2) had peripheral neuropathy due to other causes (e.g., diabetes, central nervous system malignancy, vitamin deficiency, hereditary causes, nerve compression injury), and (3) had comorbidities that impaired their ability to perform the tasks requested by the questionnaire.

Recruitment and Data Collection

Trained study staff identified potentially eligible participants via chart review and consultation with the pharmacist and the patients' oncology provider. Before attempting to consent a patient to the study, study staff confirmed eligibility using a checklist outlining each element of the inclusion and exclusion criteria. Potentially eligible participants were approached in the clinic setting by study staff and asked standardized, age-appropriate screening questions to verify the presence of CIPN signs or symptoms (e.g., numbness, tingling, difficulty walking). If the child (or guardian) reported CIPN signs/symptoms and indicated willingness to participate, study staff proceeded with the consent process.

A member of the study team explained the benefits and risks of study participation to eligible participants, and/or to a legal guardian. If willing, participant and legal representative signed and dated the consent/assent form before any study activities began. Since Bruininks–Oseretsky Test of Motor Proficiency (BOTMP) assessments were added to the data collection procedures approximately 1 year after initial study activation, previous participants at the University of Michigan if still eligible and willing to complete the P-CIN prototype 2 and the BOTMP assessment, were reconsented.

Eligible and consented/assented children completed the P-CIN using a tablet computer (or via pen and paper if the tablet computer malfunctioned) in outpatient or inpatient hematology/oncology clinical settings, after which additional examinations using the ped-mTNS or the BOTMP were conducted by study staff. Examiners were blinded to P-CIN results.

Data Management

Prospectively collected data from the electronic surveys were automatically de-identified and stored in Qualtrics (Provo, Utah, USA), a secure cloud-based platform. Paper copy research files were locked in a secure office.

Measures

Study staff collected demographic, disease, and treatment-related data from the medical record and parent interviews: the child's age, gender, race, ethnicity, education, cancer diagnosis, chemotherapy type, and time since completion of the last chemotherapy treatment.

The P-CIN

The first P-CIN prototype consisted of 14 items (Table 1) and was designed to be administered electronically on a tablet computer. Four items were used to rate CIPN symptoms—numbness and tingling in the hands and feet—experienced *today*. If the child indicated that they had experienced these symptoms, branching logic led the child to four additional questions about painful numbness and tingling. Six items were used to rate the child's ability to perform a functional task that can be negatively influenced by CIPN, such as picking up a coin or heel-walking. The child performed the task and then immediately rated the difficulty of that task (*Was that hard to do?*). Item responses ranged from 0 to 5 and were obtained using a 6-point Faces Scale© (Sanchez-Rodriguez et al.,

Table 1. Pediatric Chemotherapy-Induced Neuropathy Items.

Prototype 1 items	Prototype 2 items
1. Has it felt like pins and needles are poking your **fingers**?	No change
1a. Does it hurt when it feels like pins and needles are poking your **fingers**?	No change
2. Has it felt like pins and needles are poking your **toes**?	No change
2a. Does it hurt when it feels like pins and needles are poking your **toes**?	No change
3. Have your **fingers** felt numb or asleep?	No change
3a. Does it hurt when your **fingers** feel numb or fall asleep?	No change
4. Have your **toes** felt numb or asleep?	No change
4a. Does it hurt when your toes feel numb or fall asleep?	No change
STOP!	No change
Now we're going to ask you to do a few things. Please get four pennies and a timer before you read and answer the next questions. You can use a cellphone for the timer. Do the action before you answer the question.	
5. Squeeze someone's hand as hard as you can. Does your hand feel weak?	No change
6. Pick up a coin (dime or penny) right now. Was this hard to do?	6. Pick up a penny with one hand. Grab it with your other hand. Then put it on the table. Do this as fast as you can with the other three pennies. Was this hard to do?
7. Stand up, close your eyes, and count to 5. Did you feel like you might fall down?	7. *For the next question, you will stand on one leg with your eyes closed. Set your timer for 15 seconds but don't start it. If you don't know how, ask an adult to help you.* Start the timer. Right away, stand on one leg and close your eyes. Stop when the time is up. Did you feel like you might fall down?
8. Walk on your heels for 5 steps. Was this hard to do?	8. Walk on your heels for 10 steps. Was this hard to do?
9. Sit on the floor. Stand up without using your arms. Was this hard to do?	No change
10. Touch something icy. Does it feel cold?	Deleted

2015; Figure 1). Higher scores (sadder faces; except for Item 14 [touching something icy]) indicated more severe CIPN. Children also had the option of selecting *I don't know*. If needed, an adult was allowed to read the P-CIN survey questions to the child; research assistants recorded the child's ability to read/complete the survey independently (0 = *independent*; 1 = *required assistance*). The final question asked the child to touch something icy and rate its coldness; this question did not incorporate the Faces Pain Scale, was reverse-coded, and was preceded by a red stop sign image and the statement *Here's the last question. It's a little different from the others!* Answering *no* or selecting the happy face indicated that the child experienced severe sensory neuropathy in the fingers with an inability to sense coldness. Item scores were summed to obtain a total score ranging from 0 to 70. The Flesch–Kincaid readability score of the P-CIN is first-grade level (6-7 years old).

Preliminary testing of the first P-CIN prototype revealed floor effects (low mean scores) for three items that evaluate functional capabilities: picking up a coin (Item 6), standing with eyes closed (Item 7), and heel-walking (Item 8). After discussion among clinical and research experts, it was determined that the functional tasks may have been too easy to perform, even for children with CIPN. Therefore, we revised the three items to make the functional tasks more difficult, resulting in the P-CIN prototype 2.

The ped-mTNS

Children who were recruited at the Children's Minnesota Cancer and Blood Disorders Center ($n = 26$) underwent a neurologic examination using the ped-mTNS, which is a validated eight-item composite measure used by trained assessors to quantify CIPN signs and symptoms in children (Gilchrist et al., 2009; Gilchrist et al., 2014; Gilchrist & Tanner, 2013, 2018). The examiner used a scripted interview to evaluate and grade distal-to-proximal extension of sensory symptoms, the perceived difficulty of motor tasks, and autonomic symptom frequency. Light touch sensation was quantified using Semmes–Weinstein monofilaments

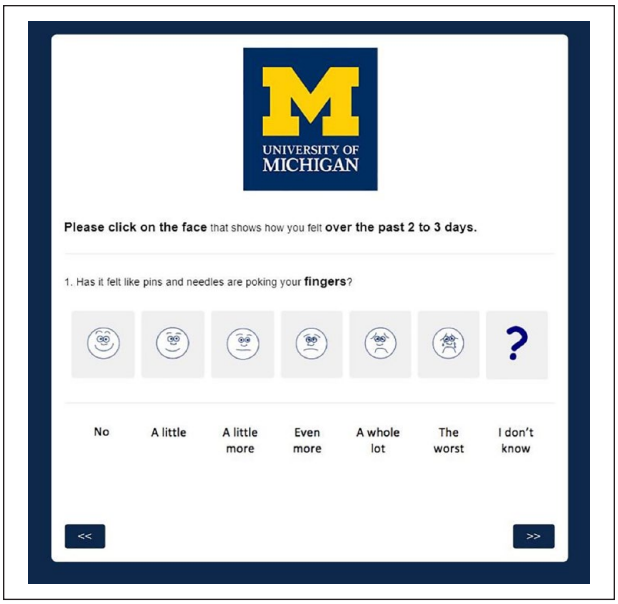

Figure 1. Pediatric Chemotherapy-Induced Neuropathy graphics.

(Rolyan-Ability One, Wisconsin, USA), pin (sharp/dull) sensation using a MediPin™ (Medipin Ltd, Hertfordshire, UK), and vibration sensations using a biothesiometer (a quantitative vibration assessment device; Biothesiometer, Ohio, USA). Deep tendon reflexes and strength in fingers, wrists, toes, and ankles were evaluated by manual muscle tests using established Medical Research Council guidelines (Matthews, 1977). The eight items were each scored from 0 to 4 and summed to obtain a score ranging from 0 to 32. Higher scores indicated worse CIPN.

The BOTMP

A subset ($n = 6$) of children recruited at the University of Michigan Cancer Center who completed the P-CIN survey prototype 2 also underwent BOTMP short version (14 items; 2nd edition) assessments (Bruininks & Bruininks, 2005). BOTMP short version scores are strongly correlated ($\sim r = .80$) with scores for the full 53-item version. Total scores range from 0 to 88, which are then presented in standardized percentile ranks categorically described as well-above average (≥98), above average (84-97), average (18-83), below average (3-17), and well-below average (≤2). The BOTMP has good interrater reliability ($r = .77$-$.97$) and test–retest reliability ($r = .86$; Wiart & Darrah, 2001). The time required to assess one individual using the short-form BOTMP varies between 15 and 20 minutes.

Fine motor function was assessed using four precision drawing exercises (scored manually using established techniques by two raters who consulted to reach consensus). Manual dexterity was scored based on how quickly the participant could transfer coins from one hand to the other in 15 seconds. Jumping and foot-tapping exercises were used to assess bilateral lower extremity coordination. Balance was tested by having participants tandem walk—in a straight line while touching the heel of one foot to the toe of the other with each step—on a line taped to the floor, and balance on one leg. Rapid hopping on one leg and dropping, catching, and dribbling a ball provided additional opportunities to test coordination. The testing ended with timed knee push-ups and sit-ups.

Statistical Analysis

Descriptive statistics ($\bar{X}$ = mean, SD = standard deviation, range) were used to describe the sample's demographic characteristics and P-CIN scores. For Aim 1, sensitivity was determined using descriptive statistics based on whether the single item scores encompassed the full score range and whether floor or ceiling effects were demonstrated by item responses clustering together in high or low categories. For Aim 2, internal consistency reliability was assessed using Cronbach's alpha and item–item correlations. Strong internal consistency reliability was indicated by an alpha coefficient ≥ .70 and item–item and item–total score correlations ranging from .30 to.70 (DeVon et al., 2007). To address Aim 3, a content validity index (CVI) was calculated using established techniques (Lynn, 1986), in which five experts—three pediatric hematologists with neuropathy expertise and two pediatric oncology nurses (one PhD- and one DNP-prepared)—evaluated the survey's content validity. These experts rated the relevance of each P-CIN item using a scale of 1 (*not relevant to pediatric CIPN*) to 4 (*very relevant and succinct*), and suggested item modifications or additional items. An excellent CVI was indicated by a score ≥ .8 (Lynn, 1986). Convergent validity (moderately strong indicated by $r \geq .3$; DeVon et al., 2007) was also assessed via correlational analyses between the P-CIN score (prototype 2) and scores from the ped-mTNS and the BOTMP (Bruininks & Bruininks, 2005). Last, clinical feasibility of the P-CIN was based on the percentage of children who could complete the measure independently: if ≥80% of the children completed the survey without adult assistance, the P-CIN was deemed a feasible measure for use in clinical practice settings.

Results

Demographics

The consort diagram (Figure 2) illustrates the number of children who were screened ($N = 307$), were deemed eligible and subsequently recruited ($N = 90$), and agreed to

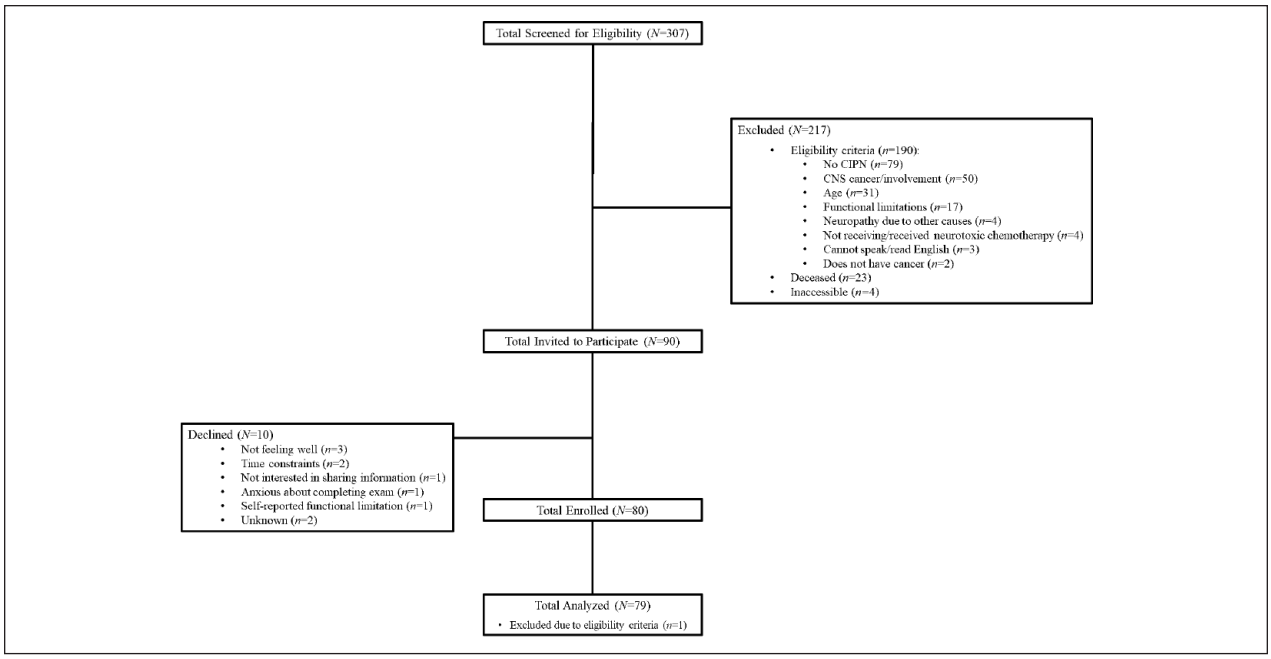

Figure 2. Flow diagram.
Note. CPIN = chemotherapy-induced peripheral neuropathy; CNS = central nervous system.

participate ($N = 80$; 89% recruitment rate). One participant was later deemed ineligible; 79 children comprised the final sample.

Sample demographic characteristics are presented in Table 2. Participants' mean age was 11.25 ($SD = 4.0$) years. Most participants were male (62%), Caucasian (86.3%), non-Hispanic (91.3%), and undergoing active treatment (81.3%) with vincristine alone (98.7%) or in combination with other neurotoxic drugs (e.g., vinblastine, carboplatin, bortezomib). Furthermore, most children had been diagnosed with acute leukemia (62.5%), but other diagnoses, including Hodgkin's (15%) and non-Hodgkin's lymphoma (11.3%), were represented within the sample.

Based on ped-mTNS scores, CIPN was mild to moderately severe ($\bar{X} = 7.58$, $SD = 4.47$); total scores ranged from 0 to 21. Of the seven subitem scores, strength ($\bar{X} = 1.15$, $SD = 0.88$) and reflex scores ($\bar{X} = 2.77$, SD 1.58) were the worst. The BOTMP total score ($\bar{X} = 63.33$, range = 48-75, $SD = 11.38$) was translated to a mean combined (including males and females) percentile rank score of 19.67 (range = 2-58, $SD = 20.64$). Half the sample ($n = 3$) exhibited average and the other half exhibited below-/well below–average motor proficiency. The tasks with the lowest scores (most difficult) were balancing on one leg ($\bar{X} = 2.50$, range = 1-4, $SD = 1.22$), hopping on one leg ($\bar{X} = 4.67$, range = 1-8, $SD = 3.01$), and performing sit-ups ($\bar{X} = 3.80$, range = 1-6, $SD = 1.92$) and knee push-ups ($\bar{X} = 3.60$, range 2-7, $SD = 2.07$).

Content Validity

CVI coefficients for the 14 P-CIN (prototype 1) items ranged from .8 to 1.0 ($p = .05$), and the instrument's overall CVI was 1.0 ($p = .05$), thereby demonstrating excellent content validity. However, content validity experts suggested a few minor revisions, which were incorporated into the survey prior to testing in the sample of pediatric patients. These suggestions included using a simpler word for numbness (i.e., asleep), mandating use of a specific type of coin when testing manual dexterity (i.e., either a penny or a dime), and changing the temporal reference from *today* to *in the past 2 to 3 days*. The rationale for this latter change was based on the clinical manifestations of painful CIPN, a type of neuropathic pain that can occur spontaneously. Defining the temporal reference as *today* could result in measurement error if the day of assessment happened to be a good day without symptoms/pain.

Item Analysis

Table 3 illustrates the results of the descriptive item analysis. For nine of 14 items, responses ranged from 0 to 4 or 5; however, response ranges for toe numbness, pick up a coin (revised), and three of four pain items were 0 to 2, suggesting floor effects. The lowest item mean score was for No. 6 (revised; pick up a coin; $\bar{X} = 0.33$, $SD = 0.82$, range = 0-2); the highest item mean score was for No. 7 (revised; standing on one leg; $\bar{X} = 2.67$, $SD = 1.21$,

Table 2. Demographic Characteristics, $N = 79$.

Variable	*M* (*SD*)
Age, years	11.25 (4)
Months since last neurotoxic chemotherapy dose	2.1 (4.9)
	N (%)
Sex	
Male	49 (62)
Female	30 (38)
Race	
Caucasian	69 (87.3)
African American	1 (1.3)
Asian	3 (3.8)
More than one race	3 (3.8)
Other	3 (3.8)
Ethnicity	
Hispanic or Latino	6 (7.6)
Not Hispanic or Latino	73 (92.4)
Cancer diagnosis	
Lymphoid leukemia	50 (63.3)
Hodgkin's lymphoma	12 (15.2)
Non-Hodgkin's lymphoma	9 (11.4)
Soft tissue	2 (2.5)
Other	6 (7.6)
Neurotoxic chemotherapy	
Vincristine	72 (91.1)
Vincristine and vinblastine	3 (3.8)
Vincristine and carboplatin	3 (3.8)
Bortezomib, vinorelbine, and brentuximab	1 (1.3)
Treatment Stage	
Actively receiving chemotherapy	65 (82.3)
Not actively receiving chemotherapy	14 (17.7)

range = 1-4). Mean scores for the three revised items included in P-CIN prototype 2 were higher than the corresponding prototype 1 item mean scores.

Internal Consistency Reliability

To calculate the item–item correlations and the Cronbach's alpha coefficient, we excluded scores from three revised items (Nos. 6, 7, and 8) in prototype 2 that were obtained by only six participants. Item–item correlations (Table 4) provide evidence of the P-CIN's internal consistency reliability. The four branching logic pain items were excluded from the item–item correlation analysis because few patients completed them. Also, pain item correlation coefficients would be difficult to interpret because scores were conditional on another item response. Correlation coefficients ranged from .01 (stand up eyes closed/tingling toes) to .62 (pick up a coin/numb fingers). Internal consistency among most items was moderately strong with correlations ranging from .31 to .62. The touch ice item (No. 10) was negatively correlated with seven of 10 items. The overall lack of correlations ≥.7 suggests no item redundancy. However, item–item correlations between most items and the sit-on-the-floor/stand (No. 9) item and the touch ice (No. 10) item were weak, suggesting that Items 9 and 10 are not internally consistent/reliable. Despite the low item–item correlations for Item 9, removing it from the survey did not improve the Cronbach's alpha coefficient. However, removing Item 10 resulted in an improved alpha coefficient of .86, which is strong evidence of the P-CIN's excellent internal consistency reliability.

Convergent Validity

P-CIN scores were strongly associated with ped-mTNS ($r = .52, p < .01$) and BOTMP ($r = -.83, p = .04$) scores. These correlational findings suggest strong convergent validity.

Feasibility

Sixty-eight percent ($n = 54$) of the study participants aged 6 to 17 completed the P-CIN questions without adult assistance; 15% ($n = 17$) of children aged 5 to 7 years could read and answer the questions independently. Children who needed assistance from a parent/guardian were younger ($\bar{X}$ age = 7.36 years, $SD = 3.15$, range = 5-17) than those who completed the measure independently ($\bar{X}$ age = 13.06 years, $SD = 2.89$, range = 6-17).

Discussion

We are not aware of any CIPN PRO measures that have been tested for use by clinicians or researchers to assess and monitor CIPN in children being treated for cancer. To address this gap, we developed and tested the first electronic CIPN PRO measure—the P-CIN—for use in quantifying CIPN subjective symptoms and functional deficits experienced by children aged 5 to 17 years who had received or were receiving neurotoxic chemotherapy at the time of the study. Specifically, we evaluated the P-CIN's sensitivity, internal consistency reliability, content and convergent validity, and clinical feasibility.

Descriptive analyses revealed floor effects (i.e., item responses did not cover the entire possible range) for several items: three of the four pain items, and the toe-numbness and pick-up-a-coin items. For the pain items, low mean scores may indicate that these items are not detecting subtle variations in pain severity. However, a more plausible explanation for the low scores could be that CIPN pain was not a prevalent problem in the sample population. This idea is supported by published results

Table 3. P-CIN Scores.

P-CIN items	*N*	*M*	*SD*	Range	
				Minimum	Maximum
1. Has it felt like pins and needles are poking your **fingers**?[a]	76	0.51	0.79	0	4
1a. Does it hurt when it feels like pins and needles are poking your **fingers**? [a]	28	0.54	0.84	0	4
2. Has it felt like pins and needles are poking your **toes**? [a]	79	0.35	0.70	0	4
2a. Does it hurt when it feels like pins and needles are poking your **toes**? [a]	20	0.60	0.50	0	1
3. Have your **fingers** felt numb or asleep? [a]	79	0.90	1.30	0	5
3a. Does it hurt when your **fingers** feel numb or fall asleep? [a]	37	0.43	0.65	0	2
4. Have your **toes** felt numb or asleep? [a]	79	0.56	0.73	0	2
4a. Does it hurt when your toes feel numb or fall asleep? [a]	33	0.42	0.61	0	2
5. Squeeze someone's hand as hard as you can. Does your hand feel weak? [a]	79	0.65	1.00	0	5
6. Pick up a coin (dime or penny) right now. Was this hard to do? [a]	73	0.14	0.54	0	3
6. (Revised) Pick up a penny with one hand. Grab it with your other hand. Then put it on the table. Do this as fast as you can with the other three pennies. Was this hard to do?	6	0.33	0.82	0	2
7. Stand up, close your eyes, and count to 5. Did you feel like you might fall down? [a]	73	0.40	0.74	0	4
7. (Revised) Start the timer. Right away, stand on one leg and close your eyes. Stop when the time is up. Did you feel like you might fall down?	6	2.67	1.21	1	4
8. Walk on your heels for 5 steps. Was this hard to do?	72	1.00	1.46	0	5
8. (Revised). Walk on your heels for 10 steps. Was this hard to do?	6	1.83	1.17	0	3
9. Sit on the floor. Stand up without using your arms. Was this hard to do? [a]	75	1.45	1.75	0	5
10. Touch something icy. Does it feel cold?	71	2.48	1.50	0	5

Note. P-CIN = Pediatric Chemotherapy-Induced Neuropathy measure.
[a]Indicates results from combined sample of participants who completed prototype 1 and prototype 2 P-CIN surveys.

from our previous study that used the same 0 to 5 scale as does the P-CIN to evaluate CIPN in children ($n = 109$) who received vincristine to treat leukemia (Lavoie Smith et al., 2015). In this prior study, painful numbness and tingling scores ($\bar{X} = 0.09$, *SD* range = 0.46-0.47, range = 0-5) were lower than the scores in the current P-CIN study. Despite attempts to increase the level of difficulty of the pick-up-a-coin item by revising the task to ask children to manipulate three coins quickly instead of just picking up a single coin, the revised item may still not have been sufficiently difficult to uncover subtle differences in task performance.

Study results also provide evidence supporting the P-CIN's strong internal consistency reliability. Removing the touch-ice item, which was confusing for the children, improved the alpha coefficient. The stand/sit item was weakly correlated ($r < .3$) with nearly all other items except for the heel-walk item. The moderately strong correlation between these two items ($r = .31$) is clinically valid because children with foot drop (assessed by the heel-walk item) may have difficulty performing the sit/stand task. Although the stand/sit item was weakly correlated with all other items, removing it did not improve the alpha coefficient. Therefore, this item should be retained and retested.

Results of this study also support the P-CIN measure's strong content and convergent validity, based on the reviews of five content experts and the P-CIN's strong correlation with the BOTMP and ped-mTNS scores. However, as previously stated, the measure's validity might be improved by revising items (e.g., increasing the difficulty of the pick-up-a-coin task/item).

As for feasibility, children from 5 to 17 years were able to read the items, perform the tasks, and answer the questions using a tablet computer. For children with reading comprehension or attention limitations, minimal support from an adult was enough to facilitate survey completion. However, 32% of children 6 to 17 years, and 85% of those ages 5 to 7 queried their parents at least once while completing the 14-item P-CIN (prototype 1),

Table 4. Pediatric Chemotherapy-Induced Neuropathy Item–Item Correlations (*n*).

Item number	1	2	3	4	5	6	7	8	9	10
1. Tingling fingers	1.00 (76)									
2. Tingling toes	.24 (76)	1.00 (79)								
3. Numbness fingers	.41 (76)	.11 (79)	1.00 (79)							
4. Numbness toes	.10 (76)	.29 (79)	.45 (79)	1.00 (79)						
5. Squeeze hand	.15 (76)	.02 (79)	.28 (79)	.26 (79)	1.00 (79)					
6. Pick up a coin	.40 (71)	.10 (73)	.62 (73)	.20 (73)	.37 (73)	1.00 (73)				
7. Stand up eyes closed	.10 (71)	.01 (73)	.52 (73)	.26 (73)	.36 (73)	.49 (73)	1.00 (73)			
8. Heel-walk	.31 (70)	.25 (72)	.09 (72)	.04 (72)	.37 (72)	.34 (72)	.12 (72)	1.00 (72)		
9. Sit on floor and stand	.23 (72)	.24 (75)	.23 (75)	.20 (75)	.16 (75)	.22 (69)	.19 (69)	.31 (69)	1.00 (75)	
10. Touch ice	.05 (69)	.10 (71)	−.19 (71)	−.23 (71)	−.15 (71)	−.13 (71)	−.24 (71)	−.10 (70)	−.21 (67)	1.00 (71)

and parents often deferred questions to recruitment staff; this may indicate a need for further revisions and more carefully scripted instructions prior to administering the survey.

Limitations

Although participants were recruited at two academic medical centers, the sample is not representative of all children who receive neurotoxic chemotherapy to treat cancer. Furthermore, the current study did not address the need for a validated measurement approach for use with very young children who have not yet learned to read or communicate verbally. Nearly all received vincristine therapy. Second, the three revised items (Nos. 6, 7, and 8) and BOTMP assessments were administered to a very small sample ($n = 6$); thus, the resultant findings should be interpreted cautiously. A third P-CIN prototype that includes these new item revisions should be retested and, once again, validated via comparisons to standardized measures of CIPN using the ped-mTNS and of motor proficiency using the BOTMP. Additionally, we did not test the full range of psychometric tests such as test–retest reliability and responsiveness to change.

Implications for Clinical Practice

Future availability of a reliable, valid, sensitive, and responsive CIPN PRO measure will facilitate significant advancements in clinical care. With a new tool such as the P-CIN, clinicians will be better able to monitor CIPN during and after cancer therapy. Researchers will have a useful outcome measure when testing future CIPN interventions in pediatric populations. The goal is to enable clinicians to use data from measures like the P-CIN to guide evidence-based decisions to modify chemotherapy doses, refer to ancillary supportive resources, and proactively institute interventions when CIPN emerges earlier or more severely than expected. The beneficial outcomes associated with better CIPN assessment will be enhanced physical, psychological, and social functioning, and decreased symptom distress and chronic suffering. When adequate CIPN monitoring enables good CIPN management, adults who survived childhood cancers will likely experience fewer CIPN-associated late effects and higher quality of life.

Conclusion

To our knowledge, the P-CIN instrument is the first PRO CIPN measure to be developed and tested in children who have received neurotoxic chemotherapy to treat cancer. Study findings suggest that the 13-item P-CIN measure is internally consistent and valid when used to quantify mainly vincristine-related CIPN. The P-CIN measure is feasible for use by children > 6 years of age within busy pediatric hematology/oncology clinical settings. Furthermore, despite the challenge of CIPN assessment for pediatric patients who have more limited ability to describe their symptoms than do adults, the new P-CIN measure has shown potential to assess and monitor CIPN with the data directly from children, without needing trained examiners. Although the instrument may be a promising new PRO measure for monitoring pediatric CIPN, these findings are preliminary given the homogeneous sample population and the small sample sizes. Further psychometric testing in larger, heterogeneous samples is necessary to strengthen the current study findings. Moreover, lack of item response variation for some items and suboptimal item–item correlations suggest that some item revisions may strengthen the instrument's psychometric properties.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Funding for this study was provided by the University of Michigan Cancer Center Health Behavior and Outcomes Program and the Pine Tree Apple Tennis Classic Foundation.

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