The Content Validity of a Chemotherapy-Induced Peripheral Neuropathy Patient-Reported Outcome Measure

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Purpose/Objectives: To test the content validity of a 16-item version of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy (QLQ-CIPN20).

Research Approach: Cross-sectional, prospective, qualitative design.

Setting: Six outpatient oncology clinics within the University of Michigan Health System's comprehensive cancer center in Ann Arbor.

Participants: 25 adults with multiple myeloma or breast, gynecologic, gastrointestinal, or head and neck malignancies experiencing peripheral neuropathy caused by neurotoxic chemotherapy.

Methodologic Approach: Cognitive interviewing methodology was used to evaluate the content validity of a 16-item version of the QLQ-CIPN20 instrument.

Findings: Minor changes were made to three questions to enhance readability. Twelve questions were revised to define unfamiliar terminology, clarify the location of neuropathy, and emphasize important aspects. One question was deleted because of clinical and conceptual redundancy with other items, as well as concerns regarding generalizability and social desirability.

Interpretation: Cognitive interviewing methodology revealed inconsistencies between patients' understanding and researchers' intent, along with points that required clarification to avoid misunderstanding.

Implications for Nursing: Patients' interpretations of the instrument's items were inconsistent with the intended meanings of the questions. One item was dropped and others were revised, resulting in greater consistency in how patients, clinicians, and researchers interpreted the items' meanings and improving the instrument's content validity. Following additional revision and psychometric testing, the QLQ-CIPN20 could evolve into a gold-standard CIPN patient-reported outcome measure.

About 64% of individuals develop chemotherapy-induced peripheral neuropathy (CIPN) following treatment with neurotoxic chemotherapeutic agents, such as taxanes, platinums, and vinca alkaloids (Seretny et al., 2014). CIPN is mainly a sensory, length-dependent neuropathy affecting sensory, motor, and autonomic peripheral nerves and is most commonly characterized by numbness, tingling, and neuropathic pain in the extremities. Symmetrical neuropathic pain; altered touch, temperature, and vibration sensibility; and diminished proprioception are characteristics of sensory CIPN, whereas motor CIPN is characterized by weakness and muscle atrophy. Diminished deep tendon reflexes indicate sensory and motor CIPN. Autonomic CIPN symptoms are less common and include constipation, orthostatic hypotension,

urinary retention, and erectile dysfunction (England et al., 2005). Most of the signs and symptoms develop initially at limb extremities and then progress distally to proximally, consistent with the known pathophysiology of a length-dependent neuropathy.

The symptoms of CIPN may negatively affect physical function and quality of life, and they may increase the risk of injury (Argyriou, Kyritsis, Makatsoris, & Kalofonos, 2014; Kautio, Haanpää, Kautiainen, Kalso, & Saarto, 2011; Mols et al., 2013; Smith et al., 2013; Tofthagen, Donovan, Morgan, Shibata, & Yeh, 2013; Tofthagen, Overcash, & Kip, 2012). For example, difficulty manipulating buttons or zippers may cause inability to dress without assistance. Patients may also have difficulty typing, playing an instrument, using eating utensils, or picking up small objects, such as coins; such losses of independence and function can affect quality of life in the physical and psychological domains. Severe symptoms, particularly painful CIPN, are associated with sleep disturbance and psychological comorbidity (Desaulniers, 2011; Geber et al., 2013; Kautio et al., 2011; Mols et al., 2013; Smith et al., 2013; Tofthagen et al., 2013). Weakness, sensory ataxia, and diminished sensation may cause greater susceptibility to tripping, falls, ulcers, and burns, particularly in patients with diabetes (Tofthagen et al., 2012; Visovsky, Meyer, Roller, & Poppas, 2008).

Despite the known negative effects of CIPN on physical function and quality of life, the incidence and severity of CIPN is frequently underreported by patients and underassessed by clinicians (Alberti et al., 2014; Cavaletti et al., 2010; Griffith, Merkies, Hill, & Cornblath, 2010). Nurses do not routinely assess CIPN because of time constraints and because they often lack the knowledge and confidence necessary to perform an accurate CIPN assessment (Binner, Ross, & Browner, 2011; Smith et al., 2014; Visovsky et al., 2012). Many patients do not report their CIPN symptoms because numbness, tingling, and neuropathic pain are difficult symptoms to describe. Patients may also be reluctant to distract their providers with seemingly minor concerns, and they may fear that their complaints will lead to reduction or discontinuation of life-prolonging or -saving chemotherapy treatments. However, CIPN should not be ignored because timely assessment and, if deemed necessary, chemotherapy drug and/or dose modifications may prevent the development of severe, refractory CIPN symptoms and possible permanent disability.

A Revised Instrument

Patient-reported outcome (PRO) measures are valuable tools that can help patients report their symptoms. The use of a PRO measure decreases clinician burden and may facilitate patients' engagement in their own care (Hibbard & Greene, 2013). The most extensively tested PRO measures are the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) and the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–CIPN (QLQ-CIPN20) (Griffith et al., 2010). The FACT/GOG-Ntx evaluates CIPN-associated health-related quality of life (Calhoun et al., 2003). It contains 28 core items assessing physical, emotional, social, and functional well-being and an 11-item neurotoxicity subscale assessing sensory, motor, and auditory function. Items are scored from 0 (not at all) to 4 (very much). Initially developed and tested in Europe, the 20-item QLQ-CIPN20 instrument was designed to supplement the EORTC-QLQ (Postma et al., 2005). It contains nine items assessing sensory neuropathy (tingling, numbness, shooting or burning pain, difficulty feeling the ground underfoot, temperature discrimination, hearing loss); eight items assessing motor neuropathy (cramps, manual strength/dexterity, foot drop, lower extremity weakness), and three items assessing autonomic neuropathy (dizziness, erectile dysfunction, blurred vision). Items are scored from 1 (not at all) to 4 (very much).

In the current study, the authors evaluated the content validity of a 16-item variant of the QLQ-CIPN20 (Postma et al., 2005). The QLQ-CIPN20 was tested rather than the FACT/GOG-Ntx for several reasons. First, the extensive use of the QLQ-CIPN20 in North American and European multisite trials demonstrates clinical feasibility and suggests that clinicians are already familiar with the instrument. The North Central Cancer Treatment Group conducted four multisite CIPN treatment trials using the QLQ-CIPN20 (Barton et al., 2011; Loprinzi et al., 2011, 2014; Reeves et al., 2012). In Europe, Cavaletti et al. (2013) evaluated the QLQ-CIPN20, as well as several other CIPN measures, in a large, multisite, cross-sectional study: the Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization (CI-PeriNoms) study. These two large, multisite research consortiums collected QLQ-CIPN20 data from hundreds of North American and European community sites, providing evidence that the instrument is feasible for use in diverse and multicultural clinical practice settings.

Second, preliminary evidence suggests that the QLQ-CIPN20 is a strong instrument that, with additional improvement, could become the gold-standard PRO measure. Four studies provide evidence of the QLQ-CIPN20's strong psychometric properties (Alberti et al., 2014; Cavaletti et al., 2013; Lavoie Smith et al., 2013; Postma et al., 2005). The published data provide preliminary evidence of its internal consistency and stability reliability, sensitivity, validity (structural,

convergent, discriminant), and responsiveness to change.

Lavoie Smith et al.'s (2013) psychometric analysis evaluating the QLQ-CIPN20's reliability, validity, and sensitivity demonstrated overall reliability and validity in the sensory and motor subscales of the instrument. However, results from the factor analysis indicated that the three autonomic items addressing orthostatic hypotension, blurred vision, and erectile dysfunction, as well as the hearing loss item, were not highly correlated with the other items ($r < 0.3$); they were, therefore, excluded from further testing. These four deletions yielded a revised 16-item version of the EORTC QLQ-CIPN20, and this 16-item version was further tested in the current study. In addition, Lavoie Smith et al. (2013) provided evidence that the QLQ-CIPN20 had two factors representing upper versus lower extremity symptoms and functional deficits. This two-factor structure was not conceptually consistent with Postma et al.'s (2005) previously defined three-factor (sensory, motor, and autonomic) structure. These results suggest that the instrument's structural validity is unstable and that continued revision and testing is warranted.

The purpose of the current study was to further evaluate the content validity of a 16-item CIPN20 using cognitive interviewing methodology. From this point forward, reduced versions of the CIPN20 will be referred to as the CIPN16 or the CIPN15; however, the authors are not suggesting that the instrument be renamed because it is copyrighted by the EORTC. Further international replication of the current findings would be required before instrument modifications would be considered by the EORTC.

Methods

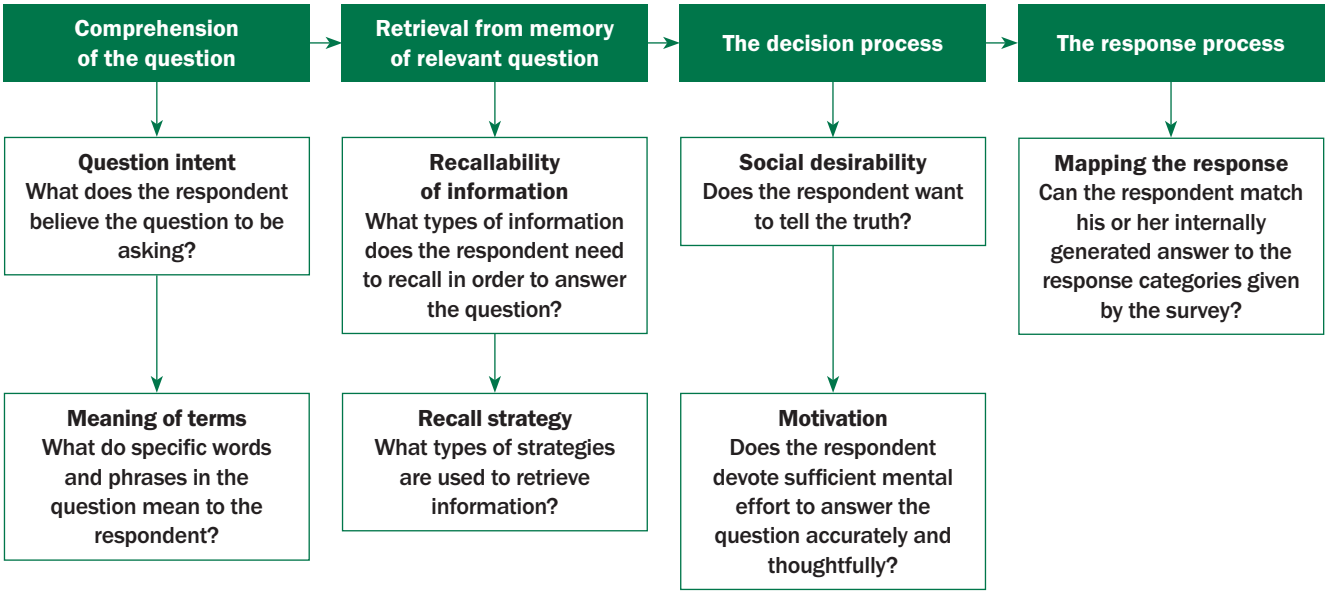
Theoretical Framework

A measure is considered to be valid when it accurately describes the underlying phenomenon or disease it is intended to measure (Waltz, Strickland, & Lenz, 2005); however, any instrument carries the possibility of measurement error, according to classical test theory (DeVellis, 2003). To reduce error, a measurement tool must undergo preliminary testing to evaluate its reliability and validity. As an initial step, cognitive interviewing methods can be used to test content validity. By encouraging respondents to think out loud about various aspects of their answers, interviewers can evaluate patients' understandings of the meaning of each item (Drennan, 2003). Because this methodology identifies potentially confusing or unclear questions that may induce measurement error, it is useful for improving item clarity, ensuring that an instrument can accurately assess the desired health outcome (Willis, 1999).

Cognitive interviewing methodology as a technique to test an instrument's content validity may be understood through the model used in Tourangeau's (1984) general cognitive theory and involves four stages (Willis, 1999) (see Figure 1). The first stage requires comprehension of the question on conceptual and literal levels; this includes question intent and the meanings of terms. To address this initial stage of thinking, the current authors asked participants to define specified words, such as "numbness" or "tingling," during the cognitive interviewing process.

Second, a response must be formulated based on the memory of relevant information. Patients may

FIGURE 1. General Cognitive Theory Model



Note. Based on information from Willis, 1999.

experience difficulty while completing this stage of thinking because they know neither how to describe their CIPN symptoms nor what to compare them to (Tofthagen, 2010). In the current study, patients were asked to describe their mental process for rating symptom severity (e.g., "What were you thinking when you rated numbness as a 1 on a 1–4 scale?"). This helped the research team to assess whether the patient was able to use relevant information when scoring CIPN severity.

Third, Tourangeau (1984) evaluates the decision process by acknowledging the potential consequences of answering a survey question (otherwise termed social desirability) and the motivation behind responding honestly (Waltz et al., 2005). Because a dishonest response is an invalid response, social desirability influences an item's validity. Social desirability was assessed in the current study by asking participants if they thought others would answer the questions honestly.

Fourth, the theory addresses the importance of the item response criteria, which, in the current study, were evaluated by patients' ability to rate their CIPN symptoms using a four-point Likert-type scale.

Participants and Setting

After this study was reviewed and approved by the University of Michigan Institutional Review Board, 25 English-speaking patients with CIPN were recruited via purposive sampling from six oncology outpatient clinics associated with the University of Michigan Health System's comprehensive cancer center in Ann Arbor, and all 25 provided signed informed consent. Patients were considered eligible if they (a) had received treatment with neurotoxic chemotherapy, (b) had established CIPN, and (c) were aged 25 years or older. Patients were excluded from study participation if they (a) had a prognosis of less than three months from study onset; (b) had peripheral neuropathy because of other causes (e.g., diabetes, alcohol abuse, CNS malignancy, vitamin deficiency, hereditary, nerve compression injury); or (c) were undergoing treatment with other nonchemotherapy neurotoxic drugs.

Procedures

Purposive sampling was used to recruit a sample representative of various genders, ethnicities, cancer diagnoses, and chemotherapeutic agents. Five cycles of semistructured cognitive interviews were conducted, with five patients per cycle (N = 25). After each cycle, the study team discussed whether the gender, ethnicity, cancer diagnosis, and chemotherapeutic agent percentages roughly represented those found in the area from which the University of Michigan Health System's comprehensive cancer center draws its patient population and determined if any subgroups should be targeted for recruitment.

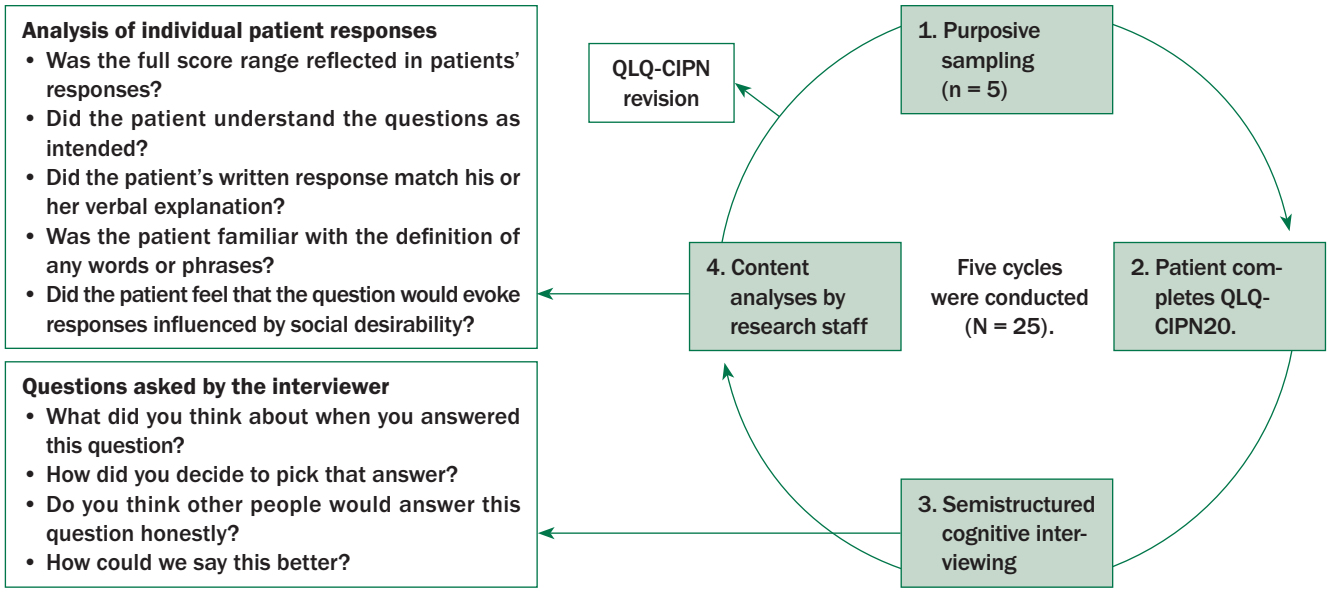
Each patient began by completing the CIPN16. After the instrument had been completed, a trained interviewer asked the patient four questions about each CIPN16 item, using established cognitive interviewing techniques (Willis, 1999).

Interviews were audio recorded but not transcribed. Per Willis's (1999) recommendations, the interviewer took notes during the interview and then, immediately following the interview, listened to the recording to verify the accuracy of those notes.

Data Analysis

The EORTC QLQ-CIPN20 was initially developed and tested in Europe. Because the EORTC requires that item revisions be appropriate for multicultural use, an international, multidisciplinary team of researchers was assembled for the current study; members met at the end of each cycle to evaluate patient responses from the cognitive interviewing process and provide input regarding the cultural relevance of all item revisions. The team consisted of three PhD-prepared nurses (one from the United States and two from Thailand), an oncology nurse practitioner, two doctoral nursing students, two undergraduate nursing students, a research assistant, a nurse project manager, and a clinical neurologist from Italy who participated in the analysis sessions via Skype. All team members had CIPN expertise obtained through either providing clinical care to patients with CIPN or working with the principal investigator on other CIPN studies during a period of many years. The neurologist had significant clinical expertise and had been involved in many CIPN clinical trials, such as the CI-PeriNoms study (Alberti et al., 2014; Cavaletti et al., 2010, 2013). In addition, she played a major role in helping the team account for differences in customs and traditions among European and North American people with CIPN.

The team began data analysis by discussing whether the sample for each cycle (n = 5) was representative of numerous demographic and disease-related variables. To evaluate for the presence of floor or ceiling effects (scores that clustered at the low or high ends of the range), the team determined whether each group of five participants used the entire 1–4 range of response options when answering each item. The researchers then analyzed whether the patients' responses demonstrated (a) understanding of the question, (b) congruence between verbal and written responses, (c) understanding of terminology, and (d) the possibility of being influenced by social desirability. Following this process, as depicted in Figure 2, the team determined which items to retain,



QLQ-CIPN20—Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy
Note. Based on information from Willis, 1999.

FIGURE 2. The Revision Process of the QLQ-CIPN20

eliminate, and/or reword. Common revisions made between cycles of cognitive interviewing included better defining ambiguous terminology, lowering the literacy level of individual items, emphasizing critical phrases by bolding, and addressing social desirability concerns. Any item that was unclear to two or more of the five participants was revised and retested using a new set of five patients. After the fifth and final round of cognitive interviewing, responses were better aligned with the intent of the questions.

Using established techniques (Lynn, 1986), content validity also was assessed using a five-person expert panel consisting of one oncologist, two nurse scientists with CIPN expertise, and two oncology nurse practitioners. The expert panel was given an explanation of the intended purpose of the instrument and asked to rate each item's relevance to CIPN using a scale ranging from 1 (not relevant) to 4 (completely relevant). A content validity index (CVI) was calculated based on experts' ratings, with 0.8–1 considered to be excellent (Lynn, 1986).

Results

Sample Characteristics

The mean age of the 25 patients was 62.08 years (SD = 9.82, median = 65 years, range = 37–75 years). Table 1 displays additional characteristics of the sample. Information about participants' education level was not collected because the instrument's readability rating was at the seventh-grade level and the authors were confident that all participants, regardless of educational background, would be able to read the instrument items.

Cognitive Interview Results and Revisions

During cognitive interviewing, patients reported challenges with the CIPN16 questions, and the research team modified the items in response to these reports. If a revised item demonstrated content validity in the next cycle of cognitive interviewing, the amended item was retained for the final version of the instrument. If not, the item was further revised and retested. After the first round of cognitive interviewing, the two questions about tingling in the fingers or hands and toes or feet and the one question about difficulty in manipulating small objects with the fingers were found to have strong content validity after minor changes to enhance readability.

A recurring theme that emerged was that many patients did not understand the difference between numbness and tingling. To address this, "loss of feeling" was added, in parentheses, after the word "numbness" to clarify. In subsequent cycles of cognitive interviewing using the revised questions, patients expressed better understanding that absence of sensation was denoted by numbness but not by tingling.

The original questions asking participants if they were experiencing shooting or burning pain in their fingers or hands and toes or feet were found to be particularly problematic because they were not prompting answers about painful peripheral neuropathy but rather generalized hand or foot pain. To address this

misunderstanding, the team reworded these questions from "Did you have shooting or burning pain in your (fingers or hands) (toes or feet)?" to "Was the numbness/tingling in your (fingers or hands) (toes or feet) painful?" In subsequent cycles of cognitive interviewing using the revised versions of these items, patients reported pain associated with peripheral neuropathy rather than pain attributable to other causes. However, in the final cycle, patients who had neither numbness nor tingling expressed uncertainty about whether to answer 1 (not at all) or to leave the item unanswered.

The questions "Did you have cramps in your (hands) (feet)?" were altered to read "Did you have cramps in your (fingers or hands) (toes or feet)?" Since these revised items were found to better reflect patient-reported symptoms of CIPN-associated cramping, the revisions were included in the final version.

A majority of patients answered the question "Did you have problems standing or walking because of difficulty feeling the ground under your feet?" based on their inability to walk or stand because of generalized weakness rather than impaired balance from CIPN. The question was altered to read "Did you have problems with balance because of numbness or tingling in your feet?" After this change, responses were much more consistently focused on the concept of neuropathy-related balance.

Generally, patients easily answered the question about difficulty distinguishing between hot and cold sensations. However, to lower the reading level by using more common words, the team replaced the phrase "difficulty distinguishing between hot and cold water" with "trouble telling the difference between hot and cold water," a recommendation suggested by one of the study participants.

Another question originally asked was "Did you have a problem holding a pen, which made writing difficult?" Although this item is relevant to CIPN, not every respondent taking the survey frequently used a writing implement. Consequently, the item was revised to inquire about the ease of using eating utensils, such as forks, spoons, and knives.

The validity of two questions ("Did you have difficulty opening a jar or bottle because of weakness in your hands?" and "Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?") was improved by substituting "trouble" for "difficulty" and bolding the phrase "because of weakness in your hands/legs." Another question was also revised to address incongruence between patient understanding and question intent. The original question asked patients if they had difficulty walking because their feet dropped downward, but this seemed to evoke responses related to walking as opposed to the intended concept of weakness and foot drop. When the question was changed to ask if the patient had "trouble flexing [his or her] ankle because of weakness," patients reported answers related to strength. A related question asked participants if they had difficulty using the pedals when driving a car. Cognitive interviewing results demonstrated that this item was asking about the same concept addressed in the question about foot drop because of weakness. In addition, many participants felt that others may not answer this question honestly because reporting trouble with driving could lead to losing driving privileges, which would limit their independence. Also noted was that, although driving a car is common in the United States, it is not necessarily so in all areas of the world. Therefore, because of concerns about item redundancy, social desirability, and global generalizability, this question was deleted.

A few patients suggested revisions to the questionnaire format. Patients reported that they would have answered the questions with less hesitation had an option representing a more neutral response between the categories "a little" and "quite a bit" been available. Respondents also reported being unsure of whether to base their responses on severity (how

TABLE 1. Sample Characteristics (N = 25)

Characteristic	n
Cancer diagnosis	
Breast	6
Myeloma	5
Pancreas	4
Colon	3
Appendiceal	1
Carcinomatosis	1
Cholangiocarcinoma	1
Endometrial	1
Gastric	1
Ovarian	1
Tonsil	1
Gender	
Female	16
Male	9
Neurotoxic agent	
Oxaliplatin	6
Paclitaxel	6
Nab-paclitaxel	4
Carboplatin and paclitaxel	3
Bortezomib	3
Docetaxel	1
Lenalidomide	1
Thalidomide	1
Race/ethnicity	
Caucasian	21
African American	3
Hispanic	1

intense symptoms were) or frequency (how often symptoms occurred). For example, one patient stated that his symptoms "happen all the time, but I don't spend all day focusing on the problem because it's not that intense."

The last step was to test the final version of the CIPN15 using established methods for calculating a CVI for each item and for the instrument overall (Lynn, 1986). CVI coefficients were 1 ($p = 0.05$) for 12 items and 0.8 for 3 items about ankle flexion and cramps in the hands and feet. The instrument's overall CVI was 0.8. These CVI results suggest adequate content validity (Lynn, 1986).

Discussion

To the authors' knowledge, no published study has explored the content validity of a reduced 16-item version of the QLQ-CIPN20 using cognitive interviewing methodology. The responses received throughout the cognitive interview process highlighted inconsistencies between how patients interpreted the questions of the CIPN16 and how the questions were intended. The study results indicate that (a) patients have difficulty quantifying CIPN symptoms, (b) patients are hesitant to report symptoms for fear of limiting independence, and (c) questionnaire design characteristics may influence patients' interpretation of questions. The item revisions that emerged from this work may result in improved reliability and validity when the CIPN15 is re-tested.

Consistent with the published literature (Alberti et al., 2014; Bridges & Smith, 2014; Cavaletti et al., 2010; Griffith et al., 2010; Lavoie Smith et al., 2013; Smith et al., 2014; Visovsky et al., 2012), the results of the current study suggest that the assessment of CIPN is often compromised because CIPN is challenging to describe and quantify. Several factors contribute to this difficulty, such as patients' ability to understand which symptoms are most relevant and how their symptoms may change over time. In addition, as one study participant pointed out, "I don't know what to compare them to."

Valid CIPN assessment may also be compromised because of social desirability. Patients may answer survey questions dishonestly because they want to present themselves in a desirable or acceptable light to their providers (Waltz et al., 2005). Social desirability was the main factor that led to removal of the question that assessed difficulty using the pedals when driving a car. Most patients said they did not think people would answer this question honestly because their responses could result in the loss of their driving privileges.

Questionnaire design characteristics, such as unfamiliar terminology and syntax, as well as exclusive response categories, may affect patients' interpretation of questions. Unfamiliar terminology or concepts may have decreased patients' understanding of some of the CIPN16 items. In this study, patients initially had difficulty understanding the difference between numbness and tingling. However, once the explanation of numbness (loss of feeling) was included in the question, patients expressed much less difficulty distinguishing between these two symptoms.

Findings from this study suggested that shorter questions were easier to understand than longer, more complex items; therefore, complex items were simplified, and, where possible, more common words were substituted for the more unusual. Patient comprehension was also improved by bolding certain phrases to draw attention to important nuances within unavoidably longer items and by modifying some items to be more consistent when referring to fingers, hands, toes, and feet. The authors anticipate that improved comprehension will translate into improved reliability and validity of the instrument.

Another source of confusion for patients using the CIPN16 pertained to the response categories for each question, a four-point Likert-type scale with the following indications: 1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much. Patients wanted a more neutral response option. However, a neutral response is sometimes intentionally avoided by instrument developers so respondents are forced to provide a substantive answer. Therefore, no changes were made to the response categories.

In addition, some participants did not understand whether the response categories were meant to measure the severity or the frequency of symptoms. Patients' confusion may be partially linked to the CIPN16 instructions for participants to "indicate the extent to which you have experienced these symptoms" on a Likert-type scale from 1 (not at all) to 4 (very much). Given that the CIPN20 is intended to measure the patient's CIPN symptom experience and associated functional limitations (Postma et al., 2005), severity and frequency are important dimensions to assess. Revising and testing the CIPN15 instructions in future studies may improve the measure.

Limitations

Because this qualitative study was conducted at a single academic institution within the United States, the results cannot be widely generalized. Also, because the sample roughly represents the demographics of the area from which the University of Michigan Health System's comprehensive cancer center draws its patients, most of the participants were non-Hispanic Caucasians. Another limitation is the preponderance of female participants attributable, in part, to the

inclusion of common female gender–specific cancers. Data were not collected about participants' education level; consequently, hypothesizing about whether the breadth and depth of participants' interview responses reflect the thoughts of people with varying educational backgrounds is not possible. Additional testing and potential revisions are required to ensure that the CIPN15 instrument is valid when used with other racial and ethnic groups. Although neuropathy signs and symptoms can vary based on the type of neurotoxic chemotherapy agent received, not all classes of these drugs were represented in this study.

Interpretation

The EORTC QLQ-CIPN20 is a valuable PRO measure that facilitates CIPN assessment. It has been translated into numerous languages and tested in populations with various cancer diagnoses and receiving a variety of neurotoxic chemotherapeutic agents. However, previous research provides evidence that a 16-item version is more reliable and valid than the original 20-item version and that the instrument's factor structure may not fall within the originally defined sensory, motor, and autonomic neuropathy domains (Lavoie Smith et al., 2013). The authors evaluated the content validity of the 16-item version and discovered discrepancies between patients' interpretations and researchers' intended meanings of the questions. These discrepancies may have compromised the instrument's validity and may partially explain the factor structure inconsistencies that have been reported in the literature (Lavoie Smith et al., 2013; Postma et al., 2005). The authors improved the CIPN16's content validity by defining unfamiliar terminology, making questions more consistent and specific, emphasizing important aspects of questions, and deleting one item that, because of social desirability, was compromising the instrument's content validity. This work resulted in a content-valid 15-item prototype that is now ready for more extensive psychometric testing.

Conclusion

CIPN is a serious condition, often resulting in chronic discomfort and decreased quality of life for millions of cancer survivors. The use of cognitive interviewing methodology in this study resulted in a modified 15-item QLQ-CIPN20 instrument. Additional research with culturally diverse patient populations is now needed for comprehensive evaluation of the modified instrument's internal consistency and stability reliability; structural, construct, convergent, and discriminant validity; sensitivity; and responsiveness to change. This work represents an initial, yet important, step in an extensive process that may ultimately lead to a gold-standard PRO measure that can be used to monitor patients in routine clinical practice settings and quantify the effect of CIPN interventions in future clinical trials.

Knowledge Translation

- Patients' interpretations of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy (QLQ-CIPN20) items were inconsistent with the intended meanings of the questions.
- Patients have difficulty quantifying symptoms of CIPN, and they may be hesitant to report symptoms for fear of consequences, such as loss of driving privileges.
- The revised 15-item version of the EORTC QLQ-CIPN20 may be a useful patient-reported outcome measure for routine assessment of CIPN in clinical and research settings.

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References

Alberti, P., Rossi, E., Cornblath, D.R., Merkies, I.S., Postma, T.J., Frigeni, B., . . . Cavaletti, G. (2014). Physician-assessed and patient-reported outcome measures in chemotherapy-induced sensory peripheral neurotoxicity: Two sides of the same coin. *Annals of Oncology, 25*, 257–264. doi:10.1093/annonc/mdt409

Argyriou, A.A., Kyritsis, A.P., Makatsoris, T., & Kalofonos, H.P. (2014). Chemotherapy-induced peripheral neuropathy in adults: A comprehensive update of the literature. *Cancer Management and Research, 6,* 135–147. doi:10.2147/CMAR.S44261

Barton, D.L., Wos, E.J., Qin, R., Mattar, B.I., Green, N.B., Lanier, K.S., . . . Loprinzi, C.L. (2011). A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Supportive Care in Cancer, 19,* 833–841. doi:10.1007/s00520-010-0911-0

Binner, M., Ross, D., & Browner, I. (2011). Chemotherapy-induced peripheral neuropathy: Assessment of oncology nurses' knowledge and practice. *Oncology Nursing Forum, 38,* 448–454. doi:10.1188/11.ONF.448-454

Bridges, C.M., & Smith, E.M. (2014). What about Alice? Peripheral neuropathy from taxane-containing treatment for advanced non-small cell lung cancer. *Supportive Care in Cancer, 22,* 2581–2592. doi:10.1007/s00520-014-2317-x

Calhoun, E.A., Welshman, E.E., Chang, C.H., Lurain, J.R., Fishman, D.A., Hunt, T.L., & Cella, D. (2003). Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *International Journal of Gynecological Cancer, 13,* 741–748. doi:10.1111/j.1525-1438.2003.13603.x

Cavaletti, G., Cornblath, D.R., Merkies, I.S., Postma, T.J., Rossi, E., Frigeni, B., . . . Valsecchi, M.G. (2013). The Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization Study: From consensus to the first validity and reliability findings. *Annals of Oncology, 24,* 454–462. doi:10.1093/annonc/mds329

Cavaletti, G., Frigeni, B., Lanzani, F., Mattavelli, L., Susani, E., Alberti,

P., . . . Bidoli, P. (2010). Chemotherapy-induced peripheral neurotoxicity assessment: A critical revision of the currently available tools. *European Journal of Cancer, 46,* 479–494. doi:10.1016/j.ejca.2009.12.008

Desaulniers, G.A. (2011). Chemotherapy induced peripheral neuropathy and subjective sleep quality in non-small cell lung cancer [Abstract 153]. *Oncology Nursing Forum, 38,* A56. doi:10.1188/11.ONF.E60

DeVellis, R.F. (2003). *Scale development: Theory and applications* (2nd ed.). Thousand Oaks, CA: Sage.

Drennan, J. (2003). Cognitive interviewing: Verbal data in the design and pretesting of questionnaires. *Journal of Advanced Nursing, 42,* 57–63. doi:10.1046/j.1365-2648.2003.02579.x

England, J.D., Gronseth, G.S., Franklin, G., Miller, R.G., Asbury, A.K., Carter, G.T., . . . Sumner, A.J. (2005). Distal symmetric polyneuropathy: A definition for clinical research: Report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology, 64,* 199–207. doi:10.1212/01.WNL.0000149522.32823.EA

Geber, C., Breimhorst, M., Burbach, B., Egenolf, C., Baier, B., Fechir, M., . . . Birklein, F. (2013). Pain in chemotherapy-induced neuropathy—More than neuropathic? *Pain, 154,* 2877–2887. doi:10.1016/j.pain.2013.08.028

Griffith, K.A., Merkies, I.S., Hill, E.E., & Cornblath, D.R. (2010). Measures of chemotherapy-induced peripheral neuropathy: A systematic review of psychometric properties. *Journal of the Peripheral Nervous System, 15,* 314–325. doi:10.1111/j.1529-8027.2010.00292.x

Hibbard, J.H., & Greene, J. (2013). What the evidence shows about patient activation: Better health outcomes and care experiences; fewer data on costs. *Health Affairs, 32,* 207–214.

Kautio, A.-L., Haanpää, M., Kautiainen, H., Kalso, E., & Saarto, T. (2011). Burden of chemotherapy-induced neuropathy—A cross-sectional study. *Supportive Care in Cancer, 19,* 1991–1996. doi:10.1007/s00520-010-1043-2

Lavoie Smith, E.M., Barton, D.L., Qin, R., Steen, P.D., Aaronson, N.K., & Loprinzi, C.L. (2013). Assessing patient-reported peripheral neuropathy: The reliability and validity of the European Organization for Research and Treatment of Cancer QLQ-CIPN20 Questionnaire. *Quality of Life Research, 22,* 2787–2799. doi:10.1007/s11136-013-0379-8

Loprinzi, C.L., Qin, R., Dakhil, S.R., Fehrenbacher, L., Flynn, K.A., Atherton, P., . . . Grothey, A. (2014). Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). *Journal of Clinical Oncology, 32,* 997–1005. doi:10.1200/JCO.2013.52.0536

Loprinzi, C.L., Reeves, B.N., Dakhil, S.R., Sloan, J.A., Wolf, S.L., Burger, K.N., . . . Lachance, D.H. (2011). Natural history of paclitaxel-associated acute pain syndrome: Prospective cohort study NCCTG N08C1. *Journal of Clinical Oncology, 29,* 1472–1478. doi:10.1200/JCO.2010.33.0308

Lynn, M.R. (1986). Determination and quantification of content validity. *Nursing Research, 35,* 382–385.

Mols, F., Beijers, T., Lemmens, V., van den Hurk, C.J., Vreugdenhil, G., & van de Poll-Franse, L.V. (2013). Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: Results from the population-based PROFILES registry. *Journal of Clinical Oncology, 31,* 2699–2707. doi:10.1200/JCO.2013.49.1514

Postma, T.J., Aaronson, N.K., Heimans, J.J., Muller, M.J., Hildebrand, J.G., Delattre, J.Y., . . . Lucey, R. (2005). The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: The QLQ-CIPN20. *European Journal of Cancer, 41,* 1135–1139. doi:10.1016/j.ejca.2005.02.012

Reeves, B.N., Dakhil, S.R., Sloan, J.A., Wolf, S.L., Burger, K.N., Kamal, A., . . . Loprinzi, C.L. (2012). Further data supporting that paclitaxel-associated acute pain syndrome is associated with development of peripheral neuropathy: North Central Cancer Treatment Group trial N08C1. *Cancer, 118,* 5171–5178. doi:10.1002/cncr.27489

Seretny, M., Currie, G.L., Sena, E.S., Ramnarine, S., Grant, R., MacLeod, M.R., . . . Fallon, M. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain, 155,* 2461–2470. doi:10.1016/j.pain.2014.09.020

Smith, E.M., Campbell, G., Tofthagen, C., Kottschade, L., Collins, M.L., Warton, C., . . . Visovsky, C. (2014). Nursing knowledge, practice patterns, and learning preferences regarding chemotherapy-induced peripheral neuropathy. *Oncology Nursing Forum, 41,* 669–679. doi:10.1188/14.ONF.669-679

Smith, E.M., Pang, H., Cirrincione, C., Fleishman, S., Paskett, E.D., Ahles, T., . . . Shapiro, C.L. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. *JAMA, 309,* 1359–1367. doi:10.1001/jama.2013.2813

Tofthagen, C. (2010). Patient perceptions associated with chemotherapy-induced peripheral neuropathy [Online exclusive]. *Clinical Journal of Oncology Nursing, 14,* E22–E28. doi:10.1188/10.CJON.E22-E28

Tofthagen, C., Donovan, K.A., Morgan, M.A., Shibata, D., & Yeh, Y. (2013). Oxaliplatin-induced peripheral neuropathy's effects on health-related quality of life of colorectal cancer survivors. *Supportive Care in Cancer, 21,* 3307–3313. doi:10.1007/s00520-013-1905-5

Tofthagen, C., Overcash, J., & Kip, K. (2012). Falls in persons with chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer, 20,* 583–589. doi:10.1007/s00520-011-1127-7

Tourangeau, R. (1984). Cognitive sciences and survey methods. In T.B. Jabine, M.L. Straf, J.M. Tanur, & R. Tourangeau (Eds.), *Cognitive aspects of survey design: Building a bridge between disciplines* (pp. 73–100). Washington, DC: National Academies Press.

Visovsky, C., Haas, M., Faiman, B., Kurtin, S., Schaftic, A.M., Lyden, E., & Rice, J. (2012). Nurse self-evaluation of assessment of chemotherapy-induced peripheral neuropathy in patients with cancer. *Journal of the Advanced Practitioner in Oncology, 3,* 319–325.

Visovsky, C., Meyer, R.R., Roller, J., & Poppas, M. (2008). Evaluation and management of peripheral neuropathy in diabetic patients with cancer. *Clinical Journal of Oncology Nursing, 12,* 243–247. doi:10.1188/08.CJON.243-247

Waltz, C.F., Strickland, O.L., & Lenz, E.R. (Eds.). (2005). *Measurement in nursing and health research* (3rd ed.). New York, NY: Springer.

Willis, G.B. (1999). *Cognitive interviewing: A "how to" guide.* Research Triangle Park, NC: Research Triangle Institute.