The Total Neuropathy Score: A Tool for Measuring Chemotherapy-Induced Peripheral Neuropathy

Ellen M. Lavoie Smith, MS, APRN-BC, AOCN®, Susan L. Beck, PhD, APRN, FAAN, and Jeffrey Cohen, MD

Purpose/Objectives: To describe the psychometric properties, clinical significance, and utility of the Total Neuropathy Score (TNS), a composite measurement tool used to assess chemotherapy-induced peripheral neuropathy (CIPN).

Data Sources: Published articles and abstracts and pertinent article references.

Data Synthesis: CIPN has been quantified inadequately because of the lack of an optimal measurement tool. The TNS is the most comprehensive composite tool to have been tested in oncology settings. The tool assesses neuropathy signs and symptoms and incorporates nerve conduction study results but inadequately assesses neuropathy-related pain severity. Seven studies have reported on the TNS's psychometric properties.

Conclusions: Initial but limited evidence supports the TNS's psychometric properties. The tool is too burdensome and inadequately assesses pain severity. Further revision and testing of the tool are recommended.

Implications for Nursing: TNS simplification and further psychometric testing could lead to future use by oncology nurses.

Comprehensive assessment of chemotherapy-induced peripheral neuropathy should be part of everyday nursing practice. Current approaches to assessment are inadequate and have contributed to the dearth of knowledge regarding true prevalence and long-term negative sequelae. Future research efforts aimed toward improvement of current measurement approaches are critically important.

Key Points . . .

- Comprehensive assessment of chemotherapy-induced peripheral neuropathy should be part of everyday nursing practice.
- Current approaches to assessment are inadequate and have contributed to the dearth of knowledge regarding true prevalence and long-term negative sequelae.
- Future research efforts aimed toward improvement of current measurement approaches are critically important.

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and distressing side effect of neurotoxic chemotherapy. It is estimated to occur in 20%–100% of patients with cancer and is a direct result of sensory, motor, and autonomic nerve injury (Armstrong, Almadrones, & Gilbert, 2005; Sweeney, 2002; Visovsky, 2003). Common characteristics of CIPN include uncomfortable and often painful sensations described as burning, numbness, stabbing, pricking, tingling, sharpness, shooting, or electric-shock-like. In most cases, neuropathy signs and symptoms first become apparent in the toes (Hausheer, Schilsy, Bain, Berghorn, & Lieberman, 2006). In this regard, it is a length-dependent phenomenon, meaning that the longest peripheral nerves are affected first (Hausheer et al.). With high cumulative chemotherapy doses, nerve fibers die back from the tips. Therefore, symptoms progress proximally from the toes to the feet, ankles, and then calves. Extension to the fingers, hands, wrists, and then arms indicates severe neuropathy and usually occurs after CIPN has been well-established in the lower extremities (Stillman & Cata, 2006). Less commonly, the autonomic nervous system may be affected, resulting in orthostatic hypotension, constipation, and difficulty with urination (Stillman & Cata). Extreme proximal extension may lead to functional disability. For example, simple daily activities such as walking, driving, or dressing can become extremely difficult and sometimes painful. Such distressing complications can continue to worsen for many months beyond treatment completion, a phenomenon referred to as coasting (Markman, 2006; Stillman & Cata). As a result, numerous patients receiving neurotoxic chemotherapeutic agents suffer with prolonged adverse effects on functional status and quality of life (QOL) (“Effects of Vinorelbine,” 1999; Ostchega, Donohue, & Fox, 1988; Wampler et al., 2006). Moreover, severe symptoms can necessitate chemotherapy dose reductions, negatively affecting cancer treatment efficacy (Hausheer et al.).

Several chemotherapeutic agents are classified as neurotoxins, the following of which are known to cause peripheral neuropathy: cisplatin, carboplatin, paclitaxel, docetaxel, etoposide, vinblastine, vincristine, oxaliplatin, thalidomide, procarbazine, cytarabine, and bortezomib (Armstrong et al., 2005; Hausheer et al., 2006; Hilkens & ven den Bent, 1997; Quasthoff & Hartung, 2002; Stillman & Cata, 2006; Verstappen, Heimans, Hoekman, & Postma, 2003). In addition to administration of a neurotoxin, several other risk factors are known to increase risk of neuropathy (see Figure 1).

Ellen M. Lavoie Smith, MS, APRN-BC, AOCN®, is the director of hematology oncology advanced practice nursing in the Norris Cotton Cancer Center at Dartmouth-Hitchcock Medical Center in Lebanon, NH, and a doctoral candidate in the Oncology PhD Distance Program in the College of Nursing at the University of Utah in Salt Lake City; Susan L. Beck, PhD, APRN, FAAN, is a professor and associate dean for academic programs in the College of Nursing at the University of Utah in Salt Lake City; and Jeffrey Cohen, MD, is a neurologist and professor in the Department of Medicine, Neurology, at the Dartmouth Medical School in Lebanon. This research was funded by an American Cancer Society doctoral scholarship (DSCN-04-161-01), a grant from the University of Utah (R21-52-CA93831), a University of Utah doctoral fellowship (SF00022835), and Cancer Center Prouty Pilot Funds. (Submitted January 2007. Accepted for publication May 12, 2007.)

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Chemotherapy-Specific Factors
- Cumulative chemotherapy dose
- High single dose
- Increased dose density (Controversy exists about whether this increases neuropathy.)
- Rapid infusion times
- Previous or concurrent use of other neurotoxic drugs

Comorbid Factors
- Hereditary or other preexisting neuropathy
- Diabetes
- Alcoholism
- HIV
- Peripheral vascular disease
- Vitamin B deficiencies

Figure 1. Neuropathy Risk Factors in Patients Receiving Chemotherapy

Note. Based on information from Haushuer et al., 2006; Hilkens & ven den Bent, 1997; Ocean & Vahdat, 2004; Quasthoff & Hartung, 2002; Verstappen et al., 2003.

Although the precise mechanism of nerve injury is not understood completely, the pathophysiology varies by neurotoxic agent and has been hypothesized for some of the aforementioned drugs. Vincas and the taxanes (e.g., paclitaxel, docetaxel) block tubulin polymerization (Haushuer et al., 2006; Ocean & Vahdat, 2004; Stillman & Cata, 2006; Verstappen et al., 2003). This leads to axonal injury and demyelination as axoplasmic transport becomes impaired because of microtubule clumping (Casey, Jellife, Le Quesne, & Millett, 1973; Guiheneuc, Ginet, Groleau, & Rojouan, 1980; Hagiwara & Sunada, 2004; Hilkens et al., 1996; Ocean & Vahdat; Verstappen et al.). Taxanes are most noted for inducing sensory neuropathy, resulting in paresthesias and dysesthesias. The drugs lead to diminished vibratory sensation and proprioception and loss of tendon reflexes because of large-fiber damage as well as altered pain and temperature sensation caused by small-fiber damage (Hilkens & ven den Bent, 1997; Hilkens et al.). Neuropathic pain can occur as a result of severe neuropathy (Ocean & Vahdat; Verstappen et al.).

Platinum analogs cisplatin, oxaliplatin, and carboplatin produce similar sensory symptoms via a common pathophysiologic mechanism (Cavaletti et al., 2001; Haushuer et al., 2006; Postma & Heimans, 1997; Screncli & McKeage, 1999; Stillman & Cata, 2006). The drugs reduce axonal transport and cause apoptosis of dorsal root ganglion cells (Cavaletti et al., 2001; Gregg et al., 1992; Hilkens & ven den Bent, 1997; Postma & Heimans; Russell, Windebank, McNiven, Brat, & Brimijoin, 1995; Screncli & McKeage; Verstappen et al., 2003). Large myelinated fibers are affected most, diminishing vibratory sensation, proprioception, and reflexes. The drugs cause mainly a sensory neuropathy, but neuropathy-related pain is uncommon.

One difference between cisplatin and oxaliplatin is that oxaliplatin can cause cold-induced paresthesias and dysesthesias of the hands, feet, and perioral and pharyngolaryngeal regions, resulting from axonal hyperexcitability (Verstappen et al., 2003). The temporal clinical pattern also varies between the two drugs. Cisplatin neuropathy can worsen for several months after treatment discontinuation. In contrast, oxaliplatin neuropathy resolves more quickly when treatment is discontinued (Screncli & McKeage, 1999). Less has been published describing carboplatin neuropathy. Although reportedly less severe, neuropathy from carboplatin can occur (Bauknecht et al., 1997; du Bois et al., 1997; Markman et al., 2001; Screncli & McKeage).

Neuropathy Measurement Overview

Comprehensive assessment of subjective and objective neurologic components, including nerve conduction studies, is the recommended gold-standard approach to neuropathy diagnostic evaluation (England et al., 2005). More specifically, a clinical examination that includes evaluation of sensation (light touch, pin-prick, vibration, and temperature), muscle strength, and deep tendon reflexes is required (Galer, 1998; Marrs & Newton, 2003). Nerve conduction studies can provide additional information regarding the neurologic function of the largest myelinated fibers through measurement of sensory and motor nerve conduction velocities and action potential amplitudes (Galer, 1998). However, nerve conduction studies have several limitations. First, they have not been shown to correlate consistently with subjective report of symptoms (England et al.). For example, in the case of small-fiber neuropathy, neurologic pain is the primary symptom. Because nerve conduction studies assess only the largest, fastest myelinated nerve fibers, results of conduction studies may be normal in the setting of small-fiber injury (England et al.). In addition, nerve conduction studies are time consuming, require subspecialty expertise to execute and interpret, and are expensive.

Vibratory and thermal sensation can be measured either by assessing a patient’s ability to feel a vibrating (128 Hz) or very cold tuning fork. Neurologists may use a specialized Rydel-Seiffer graduated tuning fork, which allows for more objective scoring (Pestronk et al., 2004). However, a standard tuning fork is adequate for use by non-neurologists. Sophisticated, computerized, quantitative sensory testing (assessment of vibratory and thermal sensation using computerized equipment) also has been used. However, because of poor reliability, quantitative sensory testing is not favored universally (Ruppert & Croarkin, 2003).

Neuropathy Measurement Challenges

Overshadowing what is believed to be the gold-standard approach are three CIPN-related measurement challenges. The first challenge is that patients often struggle with how best to describe the uncomfortable sensation, especially when it is severe enough to be characterized as painful (Galer, 1995; Smith, Whedon, & Bookbinder, 2002). As a result, analogies specific to neuropathic pain often are not initiated. Smith et al. surveyed 33 patients at a comprehensive cancer center and found that 21% reported pain from CIPN. Of great concern, patients did not report painful neuropathy during general pain screening. Patients may be reluctant to report symptoms out of concern that their symptom reports may necessitate dose reductions of potentially life-saving chemotherapeutic medications (Markman, 2006). Therefore, because patients may not report CIPN and related pain without being prompted, oncology practitioners must include neuropathy and neuropathic pain assessment in routine clinical practice.

The second challenge to neuropathy measurement is that CIPN has not been considered a side effect worthy of attention. Until recently, most oncology practitioners considered CIPN to be a minor problem that resolved over time and
seldom led to profound limitations (Marrs & Newton, 2003; Smith et al., 2002). When CIPN assessment does occur, oncology practitioners most often grade neuropathy severity using one of several toxicity grading scales, such as the National Cancer Institute Common Terminology Criteria or the Eastern Cooperative Oncology Group or Ajani grading scales. Postma et al. (1998) evaluated the differences among the grading systems, as well as physician interpretation variability, and found several inconsistencies among the scales. The scales lack adequate sensitivity to detect slight changes in neuropathy as a result of their broad scoring systems, and neuropathy signs and symptoms may be combined into one grading category. For example, reflexes and paresthesias are combined into one grading category. This is problematic because when tendon reflexes are impaired in the absence of other clinical signs or symptoms, this is indicative of early, preclinical, and less severe nerve damage. However, if both paresthesias and reflexes are abnormal, neuropathy should be graded as more severe. Combining reflexes and paresthesias diminishes a scale’s precision. Despite the problems, grading scales continue to be accepted in clinical and research settings, mainly because of their ease of use. More convincing evidence of the inadequate validity of grading scales is needed before their use will be abandoned.

The final challenge to neuropathy measurement is that a simple yet comprehensive, clinically useful, and cliniometrically sound CIPN-specific measurement tool has not been developed. Systematic scoring of the various signs and symptoms has been attempted through the development and testing of several composite instruments. Some of the instruments provide a comprehensive assessment of multiple neuropathy signs and symptoms, whereas others assess only a patient’s subjective symptoms (Bril, 1999; Chaudhry, Rowinsky, Sartorius, Donehower, & Cornblath, 1994; Dyck, Kahs, O’Brien, & Swanson, 1986; Feldman & Stevens, 1994; Franse, Valk, Dekker, Heine, & van Eijk, 2000). Others provide information regarding neuropathy-related changes in QOL or functional status (Almadrones, McGuire, Walczak, Florio, & Tian, 2004; Calhoun et al., 2003; Cella, Peterman, Hudgens, Webster, & Socinski, 2003, Kopec et al., 2006; Postma et al., 2005; Villeikyte et al., 2003). Many of the instruments have been tested only within the diabetes population.

The Total Neuropathy Score

The Total Neuropathy Score (TNS) is an instrument designed to quantify CIPN. Of all of the available neuropathy measurement tools, the TNS is the most comprehensive and, therefore, is worthy of further consideration for expanded use by oncology nurses. The TNS is the only comprehensive composite tool to assess subjective and objective aspects of peripheral nerve function and to have been tested in patients receiving neurotoxic chemotherapy. The multidimensional instrument was developed by Chaudhry et al. (1994, 1996). It assesses the presence, characteristics, and location (distally versus proximally) of symptoms, as well as the presence, severity, and location of several physical findings. The multiple versions of the TNS are compared in Table 1. Neither the full, reduced (TNSr), modified (mTNS), nor clinical (TNSc) versions adequately assess CIPN-related pain severity.

Scoring

TNS values range from 0–44 for the original version, 0–36 for the more modern TNS, 0–28 for the TNSr, 0–24 for the mTNS, and 0–28 for the TNSc. Each neuropathy item is scored by a physician or nurse on a 0–4 scale (see Table 2). The scores are summed to obtain a total score. Higher total scores correlate with more severe neuropathy. Unlike oncology grading scales (where a floor effect typically results because most neuropathy is graded 0–2), the TNS’s more finely graded scoring intervals allow for more precise detection of subtle changes in neuropathy. The wider scoring range also allows for adequate movement up or down, providing greater sensitivity.

Table 1. Versions of the Total Neuropathy Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Neuropathy Score (TNS)</th>
<th>Total Neuropathy Score–Reduced (TNSr)</th>
<th>Total Neuropathy Score–Modified (mTNS)</th>
<th>Total Neuropathy Score–Clinical (TNSc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Oncology</td>
<td>Oncology</td>
<td>Oncology</td>
<td>Oncology</td>
</tr>
<tr>
<td>Pin prick</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monofilament</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibration threshold via tuning fork</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibration threshold via QST</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermal threshold via QST</td>
<td>(omitted in modern version)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCS–sensory</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCS–motor</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep tendon reflexes</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective report</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sensory</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Motor</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Autonomic (fainting, impotence, constipation, loss of bowel and bladder control)</td>
<td>(omitted in modern version)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Based on information from Cavaletti et al., 2006 (TNSc); Chaudhry et al., 1994, 1996, 2002 (TNS and TNSr); Wampler et al., 2006 (mTNS).
Neurologic symptoms are divided into three categories: sensory, motor, and autonomic. Sensory symptom location distally to proximally is scored from 0–4 related to three subcategories: paresthesias, numbness, and neuropathic pain. A 0 score means that a patient does not have the symptom. A score of 4 is associated with symptoms extending above the knee or elbow. One flaw with the scoring approach is that proximal extension of toes and fingers is scored together, thus assuming equivalent weighting. This is not consistent with neuropathy pathophysiology because the longest, most distal nerve tips become injured first. Consequently, symptoms in the fingers typically occur later and are indicative of more severe neuropathy as opposed to signs and symptoms in the toes, which are considered earlier signs of nerve injury. Pain severity is not assessed, only its proximal extension. However, a pain score of 4 indicates disability or opioid analgesic use, a gross indicator of pain severity. Symptoms are assessed bilaterally and, if asymmetrical, the highest score is used. Then, the high score from the three subcategories serves as the final sensory symptom score. A disadvantage of grouping the three symptoms together is that a high score for paresthesias or numbness could negate a lower but clinically significant neuropathic pain score. Therefore, neuropathic pain should be scored separately so as not to be overlooked.

Neurologic signs are comprised of seven elements: sensory, motor, and autonomic. Sensory symptom location distally to proximally is scored from 0–4 related to three subcategories: paresthesias, numbness, and neuropathic pain. A 0 score means that a patient does not have the symptom. A score of 4 is associated with symptoms extending above the knee or elbow. One flaw with the scoring approach is that proximal extension of toes and fingers is scored together, thus assuming equivalent weighting. This is not consistent with neuropathy pathophysiology because the longest, most distal nerve tips become injured first. Consequently, symptoms in the fingers typically occur later and are indicative of more severe neuropathy as opposed to signs and symptoms in the toes, which are considered earlier signs of nerve injury. Pain severity is not assessed, only its proximal extension. However, a pain score of 4 indicates disability or opioid analgesic use, a gross indicator of pain severity. Symptoms are assessed bilaterally and, if asymmetrical, the highest score is used.

For nerve conduction study scoring, nerve action potential amplitudes for the right sural sensory and peroneal motor nerves are assessed. High scores (worse neuropathy) are associated with amplitudes that are lower than age-controlled norms. For example, a score of 0 correlates with nerve conduction amplitude 96% or more than what is expected for a patient’s age. In contrast, amplitudes less than 25% of age-related norms would be scored as 4. Similar to conduction study scoring, quantitative sensory testing results are scored based upon a patient’s ability to sense decreasing gradations of vibratory stimuli.

### Clinimetric Properties

Seven studies evaluated the clinimetric properties of the TNS or its alternative versions (TNSr, mTNS, TNSc) (see Table 3). Six of the studies were conducted in patients with cancer, and one was conducted in patients with diabetes. The statistical results summarized in Table 3 are limited by a lack of data reported by the original authors.

The TNS and TNSr have been shown to correlate with cumulative paclitaxel and thalidomide doses in only two suboptimal studies, providing initial but insufficient evidence of construct validity and responsiveness (Chaudhry et al., 1994, 2002). Two small sample studies did not provide evidence of TNS construct validity when correlated with platinum and suramin doses, raising concern as to whether it should be used as a generic measure of CIPN irrespective of the causative agent (Chaudhry et al., 1994, 1996). Convergent validity of the TNS and TNSc when compared to commonly used oncology neurotoxicity grading scales was demonstrated by Cavaletti et al. (2003, 2006). However, the validity of the commonly used neurotoxicity scales has been questioned. One study provided preliminary evidence of mTNS construct validity with respect to physical performance measures and taxane-related QOL (Wampler et al., 2006). Small sample

<table>
<thead>
<tr>
<th>Item</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory symptoms</td>
<td>None</td>
<td>Limited to fingers or toes</td>
<td>Extension to ankle or wrist</td>
<td>Extension to knee or elbow</td>
<td>Above knees or elbows or functionally disabling</td>
</tr>
<tr>
<td>Motor symptoms</td>
<td>None</td>
<td>Slight difficulty</td>
<td>Moderate difficulty</td>
<td>Assistance required</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>None</td>
<td>One yes</td>
<td>Two yes</td>
<td>Three yes</td>
<td>Four or five yes</td>
</tr>
<tr>
<td>Pin sensibility</td>
<td>Normal</td>
<td>Reduced in fingers or toes</td>
<td>Reduced to wrist or ankle</td>
<td>Reduced to elbow or knee</td>
<td>Reduced above elbow or knee</td>
</tr>
<tr>
<td>Vibration sensibility</td>
<td>Normal</td>
<td>Reduced in fingers or toes</td>
<td>Reduced to wrist or ankle</td>
<td>Reduced to elbow or knee</td>
<td>Reduced above elbow or knee</td>
</tr>
<tr>
<td>Strength</td>
<td>Normal</td>
<td>Mild weakness</td>
<td>Moderate weakness</td>
<td>Ankle reflex absent</td>
<td>All reflexes absent</td>
</tr>
<tr>
<td>Tendon reflexes</td>
<td>Normal</td>
<td>Ankle reflex reduced</td>
<td>Ankle reflex absent</td>
<td>Ankle reflex absent or others reduced</td>
<td></td>
</tr>
<tr>
<td>QST vibration threshold</td>
<td>Normal to &lt; 95 percentile</td>
<td>95–96 percentile</td>
<td>97 percentile</td>
<td>98 percentile</td>
<td>≥ 99 percentile</td>
</tr>
<tr>
<td>QST thermal threshold</td>
<td>Normal to &lt; 95 percentile</td>
<td>95–96 percentile</td>
<td>97 percentile</td>
<td>98 percentile</td>
<td>≥ 99 percentile</td>
</tr>
<tr>
<td>Sural amplitude score</td>
<td>Normal or reduced &lt; 5%</td>
<td>76%–95% of LLN</td>
<td>51%–75% of LLN</td>
<td>26%–50% of LLN</td>
<td>0%–25% of LLN</td>
</tr>
<tr>
<td>Peroneal amplitude score</td>
<td>Normal or reduced &lt; 10%</td>
<td>76%–95% of LLN</td>
<td>51%–75% of LLN</td>
<td>26%–50% of LLN</td>
<td>0%–25% of LLN</td>
</tr>
</tbody>
</table>

LLN—lower limit of normal; QST—quantitative sensory testing

*Note.* Based on information from Chaudhry et al., 1996, 2002.
sizes, methodologic and statistical limitations, and lack of control for confounding variables threatened the internal, external, and statistical validity of most of the studies. Cornblath et al. (1999) was the strongest of the seven, providing support through the employment of rigorous research methods for TNS reliability and validity, but only in the diabetes population. Finally, none of the aforementioned studies adequately evaluated neuropathic pain severity as a component of CIPN assessment.

### Clinical Significance and Utility

Clinical significance was addressed only briefly in one article (Chaudhry et al., 1996). Although readers could assume that clinical significance was determined through consensus of the various neurologists involved in the research, a process of that nature was not described. No evidence was presented describing how patient input has or should be obtained in that regard. Perhaps future measurement approaches should assess neuropathy-specific patient distress.

### Table 3. Studies That Evaluated the Clinimetric Properties of Versions of the Total Neuropathy Score

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Neurotoxic Agent</th>
<th>N</th>
<th>Reliability Statistics</th>
<th>Validity Statistics</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaudhry et al., 1994 (TNS)</td>
<td>Cancer (solid tumors)</td>
<td>Paclitaxel, Cisplatin</td>
<td>21</td>
<td>–</td>
<td>r = 0.62, p &lt; 0.003</td>
<td>TNS correlated with paclitaxel dose</td>
<td>Construct validity; sensitivity to change over time</td>
</tr>
<tr>
<td>Chaudhry et al., 1996 (TNS)</td>
<td>Prostate cancer</td>
<td>Suramin</td>
<td>22</td>
<td>–</td>
<td>Not reported</td>
<td>No correlation of TNS with suramin dose</td>
<td>TNS &gt; 5 defined as clinically significant</td>
</tr>
<tr>
<td>Cornblath et al., 1999 (TNS)</td>
<td>Patients with diabetes and healthy controls</td>
<td>–</td>
<td>30/5</td>
<td>ANOVA: inter-rater r = 0.86, intrarater r = 0.89</td>
<td>CI = 95%</td>
<td>Tool stability and equivalence demonstrated; correlated with two diabetes neuropathy measures</td>
<td>Intra- and inter-rater reliability plus convergent validity</td>
</tr>
<tr>
<td>Chaudhry et al., 2002 (TNS without QST)</td>
<td>Cancer; bone marrow transplantation (4)</td>
<td>Thalidomide</td>
<td>7</td>
<td>–</td>
<td>r = 0.83, p not reported</td>
<td>Correlated with thalidomide dose; responsiveness not determined because of lack of control group measurement</td>
<td>Results suggesting construct validity compromised by small N and heterogeneous population</td>
</tr>
<tr>
<td>Cavaletti et al., 2003 (TNS and TNSr)</td>
<td>Cervical cancer</td>
<td>Paclitaxel, Cisplatin</td>
<td>60</td>
<td>–</td>
<td>TNS ≥ 5: r = 0.187–0.220, p not significant TNS &lt; 5: r = 0.472–0.691, p ≤ 0.0001 TNS/TNSr r = 0.937–0.944, p &lt; 0.0001</td>
<td>Correlated with NCI-CTC, ECOG grading scales only with TNS and TNSr &lt; 5; TNS and TNSr correlated with each other</td>
<td>Construct validity not demonstrated because compared to untested construct</td>
</tr>
<tr>
<td>Cavaletti et al., 2006 (TNSr and TNSc)</td>
<td>A variety of solid and hematologic cancers</td>
<td>Cisplatin, Carboplatin, Paclitaxel, Docetaxel, Thalidomide, Vincristine, Vinblastine</td>
<td>428</td>
<td>Inter-rater concordance = 92%</td>
<td>TNSr and NCI-CTC/ECOG sensory (r = 0.738, 0.709) TNSr and NCI-CTC/ECOG sensory (r = 0.666, 0.747) TNSr/TNSc and NCI-CTC/ECOG motor scores ranged from 0.492–0.518, All p &lt; 0.0001</td>
<td>TNSr and TNSc correlated with sensory grading scales, but moderate to low correlation with motor-grading scales; sensory and motor symptoms, NCS, and pin and vibration sensitivity were moderately to poorly correlated with grading scale scores (r = 0.316–0.577)</td>
<td>Diverse and large sample size is a study strength. Lack of control for many confounding variables. TNSr and TNSc compared to untested construct</td>
</tr>
<tr>
<td>Wampler et al., 2008 (TNS and mTNS)</td>
<td>Breast cancer and healthy controls</td>
<td>Paclitaxel, Docetaxel</td>
<td>20/20</td>
<td>–</td>
<td>r = 0.990, p &lt; 0.001 r = –0.638, 0.654, –0.615, p = 0.002–0.004 p &lt; 0.001</td>
<td>TNS correlated with mTNS; mTNS correlated with balance, physical performance, and quality of life and discriminated between cancer and healthy controls.</td>
<td>Suggests mTNS construct validity and no added benefit from NCSs; threats to statistical and external validity</td>
</tr>
</tbody>
</table>

ANOVA—analysis of variance; CI—confidence interval; ECOG—Eastern Cooperative Oncology Group; mTNS—Total Neuropathy Score–modified; NCI-CTC—National Cancer Institute Common Terminology Criteria; NCS—nerve conduction studies; QST—quantitative sensory testing; TNS—Total Neuropathy Score; TNSc—Total Neuropathy Score–clinical; TNSr—Total Neuropathy Score—reduced.
Sensitivity and responsiveness are additional qualities to consider. As previously mentioned, TNS sensitivity to detect subtle changes in peripheral nerve function far surpasses that of the commonly used neurotoxicity grading scales. Also, some evidence exists that the TNS is responsive to changes over time in patients receiving higher and higher cumulative neurotoxic chemotherapy doses. An additional factor that should be considered is whether the TNS is practical for use by non-neurologists employed in busy oncology settings. No studies to date have assessed physician or nurse inter-rater reliability when compared to a neurologist.

**Application to Nursing Practice**

The TNS was designed for use by a neurologist when assessing neuropathy signs and symptoms. No literature was found that reported TNS use by nurses. However, the most clinically applicable TNS variant, the TNSc, could be employed easily by nurses with only minimal specialized training. Although basic physical assessment training for nurses typically incorporates subjective symptoms, pinprick sensation, and muscle strength, most nurses are less skilled at assessing vibratory sensation and tendon reflexes. However, those skills can be learned easily. The following example illustrates the simplicity of vibration sensation evaluation techniques. When assessing tuning fork vibration sensitivity, a nurse’s ability to sense vibration is contrasted against that of a patient. While placing the vibrating tuning fork on a patient’s great toe metatarsal or fingernail, a nurse then would place his or her own finger beneath the patient’s great toe or finger, feeling the vibration through the patient’s digit. The nurse should feel the vibration for as long as the patient feels it. However, if the patient stops feeling vibration before the nurse, this indicates that the patient’s vibratory sensitivity is diminished. Tendon reflexes are more challenging to assess, particularly the ankle reflex. However, with practice, nurses can become skilled at reflex assessment. One way to facilitate neuropathy assessment training would be to routinely offer neuropathy educational sessions at the Oncology Nursing Society’s semianual conferences.

**Recommendations for Future Research**

Further clinimetric research is needed, with an emphasis on developing a more parsimonious and clinically useful TNS variation. Although Cavaletti et al. (2006) evaluated the validity of the simplified TNSc in comparison with oncology grading scales, the work may have been premature. Before such comparisons can be made, future work should establish the clinimetric value of neuropathy grading scales. Otherwise, researchers may be attempting to establish validity of a new measure through comparison with a potentially invalid standard.

In addition to determining how a new tool compares with other neuropathy measurement tools, the extent to which a shortened TNS will predictably quantify neuropathy and pain in relationship to other related or similar constructs should be assessed. For example, a neuropathy tool should reveal that neuropathy and related pain are more severe in patients receiving higher cumulative and individual chemotherapy doses and in those with comorbid illnesses that place them at increased risk of developing CIPN. Additionally, future studies should investigate whether a simplified TNS can be used to quantify CIPN caused by any neurotoxic agent, regardless of drug-specific variations in nerve injury pathophysiology. Therefore, the refined TNS should be tested in patients receiving a wide range of neurotoxic agents and cumulative and individual doses, as well as in high-risk patients, because specific patterns of neuropathy may be associated with specific agents. Lastly, further research assessing whether nurses can accurately complete a shortened TNS-based neurologic assessment when compared to neurologists will be important.

**Conclusion**

As new cancer treatments using neurotoxic agents ultimately prolong life, the effect of chronic, disabling neuropathy will become even more apparent. Yet intervention research targeting CIPN prevention and treatment has been hindered by the absence of a simple, clinically useful, and psychometrically sound measurement tool that can be used by oncology nurses. The development of such a tool will lead to improved neuropathy assessment and will facilitate discovery of future interventions. Therefore, CIPN measurement research should be a priority for the future.

**Author Contact:** Ellen M. Lavoie Smith, MS, APRN-BC, AOCN®, can be reached at ellen.l.smith@hitchcock.org, with copy to editor at ONFEditor@ons.org.

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