Article

Current Methods for the Assessment and Management of Taxane-Related Neuropathy

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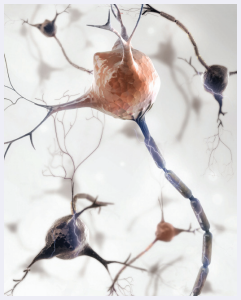

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Taxane-induced peripheral neuropathy (TIPN) affects a number of patients with breast cancer. To properly manage these patients, nurses must be able to identify and assess TIPN, as well as educate patients on TIPN as a side effect of taxane therapy. This article provides practical suggestions regarding how nurses can incorporate clinically feasible measurement approaches into practice and includes examples of grading TIPN that illustrate the limitations of the current tools and techniques for assessment. For example, a shortened and revised version of the Total Neuropathy Score and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity subscale should be considered for future use. In addition, neuropathy-related results from numerous phase III trials in breast cancer are discussed, and the latest evidence regarding pharmacologic interventions for TIPN is briefly summarized.

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Taxane-induced peripheral neuropathy (TIPN) significantly compromises the quality of life of breast cancer survivors. TIPN is an underrecognized problem because of continued reliance on suboptimal assessment approaches. Emerging empirical evidence suggests that more reliable, valid, sensitive, and clinically feasible TIPN measurement approaches should be used to quantify TIPN in clinical and research settings (Cavaletti et al., 2010; Griffith, Merkies, Hill, & Cornblath, 2010). Oncology nurses know that TIPN poses significant problems for patients with breast cancer. Although most oncology nurses are well versed regarding TIPN signs, symptoms, and related adverse outcomes, this knowledge does not necessarily translate into knowing what to do about it. Measurement approaches should include objective assessment of peripheral neuropathy signs and symptoms using history taking and simple physical examination approaches. TIPN signs and symptoms can be quantified using a composite measure such as the revised and shortened Total Neuropathy Score (TNS) (Chaudhry, Rowinsky, Sartorius, Donehower, & Cornblath, 1994; Cornblath et al., 1999; Lavoie Smith, Cohen, Pett, & Beck, 2011; Smith, Beck, & Cohen, 2008; Smith, Cohen, Pett, & Beck, 2010). In addition, patient-reported outcome measures should be used to assess the patient's experience and the short 11-item Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) subscale often is used because of its excellent psychometric properties (Griffith et al., 2010). To date, duloxetine is the only pharmacologic intervention tested via a large phase III trial that has been shown to be effective in diminishing TIPN-related pain. Future testing of additional pharmacologic and nonpharmacologic interventions is needed.

Pathophysiology

Taxane chemotherapy (paclitaxel, docetaxel, and *nab*-paclitaxel) has led to significant improvements in breast cancer survival in patients with metastatic breast cancer. However, in addition to killing cancer cells, taxanes cause unwanted damage to the nerve cell axon and surrounding myelin sheath and the cell body within the dorsal root ganglion (Argyriou, Koltzenburg, Polychronopoulos,

Papapetropoulos, & Kalofonos, 2008). Although the precise TIPN pathophysiologic mechanism is unknown, taxanes are believed to exert their neurotoxic effects on peripheral nerves by stabilizing the microtubule system critical for mitosis and intracellular transport of proteins and other substances between the axon and the cell body (Argyriou et al., 2008; Carlson & Ocean, 2011; Swain & Arezzo, 2008; Theiss & Meller, 2000). Once the microtubule transport system becomes damaged, the cell undergoes apoptosis (programmed cellular death) (Carlson & Ocean, 2011). Mitochondrial swelling, damage to peripheral nerve support structures, and various immune mechanisms have been implicated in the development of painful TIPN (Flatters & Bennett, 2006; Peters et al., 2007; Polomano, Mannes, Clark, & Bennett, 2001; Siau, Xiao, & Bennett, 2006; Zheng, Xiao, & Bennett, 2011). In addition, the Cremophor® EL (polyoxyethylated castor oil; now renamed as Kolliphor® EL) solvent used to formulate paclitaxel may contribute to TIPN, but a definitive causal relationship has not been established (Authier, Gillet, Fialip, Eschalier, & Coudore, 2000; Gradishar et al., 2005; Hausheer, Schilsky, Bain, Berghorn, & Lieberman, 2006; Swain & Arezzo, 2008).

Clinical Manifestations

TIPN is generally described as a symmetrical "dying back" phenomenon, meaning that the tips of the longest nerves are affected first. That explains why most patients initially report TIPN symptoms in their toes. As an individual receives higher cumulative taxane doses, symptoms extend up the feet to the ankles and lower legs and eventually appear in the fingertips, hands, wrists, and arms. Although all peripheral nerve types (sensory, motor, and autonomic) can be damaged as a result of taxane therapy, large, myelinated sensory nerve fibers are the most vulnerable (Argyriou et al., 2008; Carlson & Ocean, 2011). Common sensory symptoms include numbness, tingling, electric shock-like sensations, neuropathic pain, and impaired balance from diminished plantar sensation and resultant altered proprioception (Kuroi & Shimozuma, 2004; Swain & Arezzo, 2008; Wickham, 2007). Patients typically compensate for balance impairment by broadening their gate and using visual, rather than sensory, clues when monitoring foot placement. Impaired sensation in the fingertips can compromise the ability to manipulate small objects, button or zip clothing, or perform other daily tasks. Patients occasionally report mechanical or temperature-induced injuries. Those injuries occur when TIPN-related numbness impairs the patient's ability to sense sharp objects or extremely hot or cold temperatures. Occurring in about 25%–30% of patients, painful peripheral neuropathy can be particularly distressing (Loprinzi et al., 2011; Smith et al., 2010). One type of neuropathy-related pain, allodynia, occurs when pain results from nonpainful stimuli. For example, patients may report pain when bed sheets touch their feet or when attempting to wear common clothing items, such as socks, shoes, or gloves.

TIPN signs include diminished or absent reflexes as well as altered vibration, temperature, and pin sensibility. Those TIPN signs are detectable only via physical examination and may appear earlier than subjective symptoms. As such, patients may not notice these TIPN signs before a clinician detects the deficit during a physical examination. This emphasizes the importance of the clinical examination because detection of preclinical signs (occurring early and before the emergence of patient-reported symptoms) can provide evidence that TIPN is worsening before the patient is aware that a problem exists. Although less common, upper and lower extremity motor weakness can occur. Motor weakness is typically evidenced when the patient is, for example, unable to turn on or off sink faucets, reports frequent tripping and falls, has difficulty managing a vehicle's gas and brake pedals, or when a foot drop becomes noticeable. Autonomic neuropathy symptoms (e.g., constipation, erectile dysfunction, orthostatic hypotension, urinary retention) also occur, albeit infrequently. Autonomic symptoms are more difficult to attribute to TIPN because of the presence of other comorbid conditions or concurrent mediations that can lead to similar problems. Lastly, paclitaxel acute pain syndrome is characterized by moderate to severe pain in the back, hips, shoulders, thighs, and legs occurring during the first week following paclitaxel administration (Loprinzi et al., 2011). The symptoms of paclitaxel acute pain syndrome have been described as affecting the muscles and joints, but evidence suggests that this pain is instead because of taxane-related nerve injury (Loprinzi et al., 2011).

Measurement

TIPN incidence data from breast cancer phase III studies are quite variable. Table 1 presents data demonstrating that TIPN incidence rates reported in phase III trials of metastatic and adjuvant populations conducted since the mid-2000s range from 8%–83%. The majority of patients with metastatic breast cancer included in these trials had previously received a neurotoxic agent. Unless otherwise indicated, TIPN was quantified using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Higher TIPN incidence and severity are generally associated with more frequent taxane administration and higher cumulative dosages. However, incidence rates vary greatly across studies when comparisons are made of TIPN caused by the same taxane with the same dose and treatment schedules. What might explain these discrepancies? The wide range in reported incidence is partially attributable to the presence or absence of various factors known to influence the risk of developing TIPN, such as taxane type, the dose administered (M^2), cumulative dosage, and dose density, as well as demographic, genetic, and comorbid variables (Bergmann et al., 2011; Hausheer et al., 2006; Hertz et al., 2012; Kroetz et al., 2010; Schneider et al., 2011; Sissung et al., 2006; Visovsky, Meyer, Roller, & Poppas, 2008; Windebank & Grisold, 2008). However, another important factor influencing the imprecise understanding regarding the scope of the problem relates

Exploration on the Go

The Putting Evidence Into Practice resource offers additional information on peripheral neuropathy. To access, open a barcode scanner on your smartphone, take a photo of the code, and your phone will link automatically. Or visit www.ons.org/Research/PEP/Peripheral.

TABLE 1. Taxane-Induced Peripheral Neuropathy Incidence and Severity in Phase III Clinical Trials

Study	Sample	Taxane	Dosage	Duration	Sensory Neuropathy (%)			Motor Neuropathy (%)		
					Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Albain et al., 2008	521 previously treated patients with MBC	Paclitaxel	175 mg/m^2 every three weeks	5.7–6.4 cycles ($\bar{X}$)	17.7–18.4	3.9–5.3	0.4	2.3–6.1	0.8–2.3	0.4
Andersson et al., 2011	139 previously treated patients with locally advanced or MBC	Docetaxel	100 mg/m^2 every three weeks	0–26 cycles	18.7	30.9	0	11.5	4.3	0
Cassier et al., 2008	107 previously treated patients with MBC	Paclitaxel	175 mg/m^2 every three weeks	4 cycles	6.8[a] (grade 3 or higher)			6.8[a] (grade 3 or higher)		
	210 previously treated patients with MBC	Docetaxel	75 mg/m^2 every three weeks	4 cycles	0.9[a] (grade 3 or higher)			0.9[a] (grade 3 or higher)		
Eiermann et al., 2011	1,635 patients undergoing adjuvant treatment for MBC	Docetaxel	75 mg/m^2 every three weeks	6 cycles	Not reported	0.3 (grade 3 or higher)		Not reported		
	1,634 patients undergoing adjuvant treatment for MBC	Docetaxel	100 mg/m^2 every three weeks	4 cycles	Not reported	1.5 (grade 3 or higher)		Not reported		
Fountzilas et al., 2009	131 previously treated patients with MBC	Paclitaxel (plus carboplatin)	175 mg/m^2 every three weeks	6 cycles	5[a] (grade 3 or higher)			5[a] (grade 3 or higher)		
	134 previously treated patients with MBC	Docetaxel	75 mg/m^2 every three weeks	6 cycles	0[a] (grade 3 or higher)			0[a] (grade 3 or higher)		
	133 previously treated patients with MBC	Paclitaxel	80 mg/m^2 weekly	12 weeks	8[a] (grade 3 or higher)			8[a] (grade 3 or higher)		
Frasci et al., 2006	100 patients with locally advanced MBC	Paclitaxel (plus cisplatin)	120 mg/m^2 weekly	12 weeks	3[a,b] (grade 3 or higher)			3[a,b] (grade 3 or higher)		
	100 patients with locally advanced MBC	Paclitaxel	175 mg/m^2 every three weeks	4 cycles	0[a,b] (grade 3 or higher)			0[a,b] (grade 3 or higher)		
Gradishar et al., 2005	229 previously treated patients with MBC	*nab*-Paclitaxel	260 mg/m^2 every three weeks	56% received 6 cycles or more	Not reported	10	0	0	0	0
	225 previously treated patients with MBC	Paclitaxel	175 mg/m^2 every three weeks	50% received 6 cycles or more	Not reported	2	0	0	0	0

(Continued on the next page)

[a] Sensory versus motor was not delineated.

[b] Sensory and motor signs and symptoms are combined into one scale, rated from 0–4, with a higher score meaning worse neuropathy.

[c] PNQ scores D and E indicate moderate to severe ratings assessed at cycle 7.

MBC—metastatic breast cancer; NCI CTCAE—National Cancer Institute Common Terminology Criteria for Adverse Events; PNQ—Patient Neurotoxicity Questionnaire

TABLE 1. Taxane-Induced Peripheral Neuropathy Incidence and Severity in Phase III Clinical Trials *(Continued)*

Study	Sample	Taxane	Dosage	Duration	Sensory Neuropathy (%)			Motor Neuropathy (%)		
					Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Hamberg et al., 2011	53 previously treated patients with MBC	Docetaxel (plus concurrent trastuzumab)	100 mg/m^2 every three weeks	6 cycles	62 (grades 1–4); 8 (grade 3 or higher)			Not reported		
	46 previously treated patients with MBC	Docetaxel (following trastuzumab)	100 mg/m^2 every three weeks	6 cycles	31 (grades 1–4); 0 (grade 3 or higher)			Not reported		
Loesch et al., 2010	906 patients undergoing adjuvant treatment for MBC	Paclitaxel	175 mg/m^2 every three weeks	4 cycles	Not reported	6	Less than 1	Not reported		
	895 patients undergoing adjuvant treatment for MBC	Paclitaxel	200 mg/m^2 every three weeks followed by 80 mg/m^2 weekly	4 cycles followed by 12 weeks	Not reported	12.7	Less than 1	Not reported		
Miles et al., 2010	231 previously treated patients with locally advanced or MBC	Docetaxel	100 mg/m^2 every three weeks	42% received a maximum of 9 cycles	Not reported	2.2 (grade 3 or higher)		Not reported		
Miller et al., 2007	346 previously treated patients with locally advanced or MBC	Paclitaxel	90 mg/m^2 weekly for three of four weeks	Not reported (until progression or severe toxicity)	Not reported	17.1	0.6	Not reported		
Nielsen et al., 2011	167 previously treated patients with locally advanced or MBC	Docetaxel	75 mg/m^2 every three weeks	6 cycles (median)	9	2.4	0.6	10.8	2.4	0
	164 previously treated patients with locally advanced or MBC	Docetaxel	100 mg/m^2 every three weeks	6 cycles (median)	4.9	6.1	0	20.7	9.8	0
Nuzzo et al., 2008	48 patients, aged 65–79 year, undergoing adjuvant treatment for MBC	Docetaxel	35 mg/m^2 weekly three of every four weeks	4–6 cycles	2.1 (4.2 grade 1)	2.1	0	2.1	0	0
Piedbois et al., 2007	35 patients undergoing neoadjuvant treatment for MBC	Docetaxel	75 mg/m^2 every three weeks	6 cycles	17 (grades 1–4); 0 (grade 3 or higher)			Not reported		

(Continued on the next page)

[a] Sensory versus motor was not delineated.

[b] Sensory and motor signs and symptoms are combined into one scale, rated from 0–4, with a higher score meaning worse neuropathy.

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TABLE 1. Taxane-Induced Peripheral Neuropathy Incidence and Severity in Phase III Clinical Trials *(Continued)*

Study	Sample	Taxane	Dosage	Duration	Sensory Neuropathy (%)			Motor Neuropathy (%)		
					Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Piedbois et al., 2007	30 and 34 patients (two samples) undergoing neoadjuvant treatment for MBC	Docetaxel	100 mg/m^2 every two weeks	4 cycles	47–53 (grades 1–4); 9–10 (grade 3 or higher)			Not reported		
Rivera et al., 2008	59 previously treated patients with locally advanced or MBC	Docetaxel	75 mg/m^2 every three weeks	9.5 cycles (median)	Not reported	10% (grade 3 or higher)		Not reported		
	59 previously treated patients with locally advanced or MBC	Docetaxel	35 mg/m^2 weekly every three of four weeks	7 cycles (median)	Not reported	5% (grade 3 or higher)		Not reported		
Seidman et al., 2008	225 previously treated patients with locally advanced or MBC	Paclitaxel	175 mg/m^2 every three weeks	Not reported (until progression or severe)	21	12	0	5	4	0
	346 previously treated patients with locally advanced or MBC	Paclitaxel	80–100 mg/m^2 weekly	Not reported (until progression or severe)	21	24–30	Less than 1	8	9	0
Shimozuma et al., 2012	76 patients undergoing adjuvant treatment for MBC	Paclitaxel	175 mg/m^2 every three weeks	8 cycles	12.3[c] (grade D or higher)			NCI CTCAE or PNQ incidence totals not reported		
	75 patients undergoing adjuvant treatment for MBC	Docetaxel	75 mg/m^2 every three weeks	8 cycles	14.9[c] (grade D or higher)			NCI CTCAE or PNQ incidence totals not reported		
Untch et al., 2011	362 patients undergoing neoadjuvant treatment for MBC	Paclitaxel	175 mg/m^2 every three weeks	4 cycles	60.2 (grades 1–4); 2.5 (grade 3 or higher)			Not reported		
	352 patients undergoing neoadjuvant treatment for MBC	Paclitaxel	225 mg/m^2 every two weeks	3 cycles	81.5 (grades 1–4); 8.9 (grade 3 or higher)			Not reported		
Valero et al., 2011	131 previously treated patients with MBC	Docetaxel	100 mg/m^2 every three weeks	8 cycles	58 (grades 1–4); 3 (grade 3 or higher)			8.4 (grades 1–4); 0.8 (grade 3 or higher)		
	131 previously treated patients with MBC	Docetaxel (plus carboplatin)	75 mg/m^2 every three weeks	8 cycles	45.8 (grades 1–4); 0.8 (grade 3 or higher)			4.6 (grades 1–4); 0 (grade 3 or higher)		

(Continued on the next page)

[a] Sensory versus motor was not delineated.

[b] Sensory and motor signs and symptoms are combined into one scale, rated from 0–4, with a higher score meaning worse neuropathy.

[c] PNQ scores D and E indicate moderate to severe ratings assessed at cycle 7.

MBC—metastatic breast cancer; NCI CTCAE—National Cancer Institute Common Terminology Criteria for Adverse Events; PNQ—Patient Neurotoxicity Questionnaire

TABLE 1. Taxane-Induced Peripheral Neuropathy Incidence and Severity in Phase III Clinical Trials *(Continued)*

Study	Sample	Taxane	Dosage	Duration	Sensory Neuropathy (%)			Motor Neuropathy (%)		
					Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
von Minckwitz et al., 2008	321 patients undergoing neoadjuvant treatment for MBC	Docetaxel	75 mg/m^2 every three weeks	6 cycles	38.1 (grades 1–4); less than 1 (grade 3 or higher)			Not reported		
Winer et al., 2004	150 previously treated patients with MBC	Paclitaxel	175 mg/m^2 every three weeks	Not reported	57 (grades 1–4); 7 (grade 3 or higher)			13 (grades 1–4); 5 (grade 3 or higher)		
	152 previously treated patients with MBC	Paclitaxel	210 mg/m^2 every three weeks	Not reported	74 (grades 1–4); 19 (grade 3 or higher)			26 (grades 1–4); 11 (grade 3 or higher)		
	149 previously treated patients with MBC	Paclitaxel	250 mg/m^2 every three weeks	Not reported	83 (grades 1–4); 33 (grade 3 or higher)			30 (grades 1–4); 14 (grade 3 or higher)		

[a] Sensory versus motor was not delineated.

[b] Sensory and motor signs and symptoms are combined into one scale, rated from 0–4, with a higher score meaning worse neuropathy.

[c] PNQ scores D and E indicate moderate to severe ratings assessed at cycle 7.

MBC—metastatic breast cancer; NCI CTCAE—National Cancer Institute Common Terminology Criteria for Adverse Events; PNQ—Patient Neurotoxicity Questionnaire

to inadequate attention to TIPN measurement. Many clinicians believe that TIPN poses only a minor problem because, in most published reports, only the rates of moderate and severe (grades 3 or 4) TIPN are reported. The reporting patterns illustrate clinician bias regarding the degree of clinically important TIPN and discount the discomfort and distress potentially caused by any degree of peripheral neuropathy.

Another problem is that, in phase III studies, TIPN is most often quantified using toxicity grading scales, and these scales are known to have suboptimal reliability and validity as well as suboptimal sensitivity reflected by floor effects (low scores), leading to underrepresentation of TIPN incidence and severity (Cavaletti et al., 2010; Griffith et al., 2010; Kuroi et al., 2009; Postma et al., 1998). To illustrate the main limitations, grading of two patient examples is described here.

Clinical Examples

The first patient has reduced ankle reflexes as the only sign of peripheral neuropathy. The second patient reports paresthesias that do not interfere with activity, plus all reflexes are absent. Per NCI CTCAE, version 4, paresthesias and tendon reflex loss define grade 1 sensory neuropathy, and grades 2–4 are defined by moderate, severe, and life-threatening interference with activities of daily living. Grade 5 equates to death from peripheral neuropathy, an extremely rare event. Both patients have grade 1 TIPN according to the NCI CTCAE, but the second patient's neuropathy is more severe. This example illustrates the lack of sensitivity associated with the NCI CTCAE grading system because signs and symptoms representing a broad range of TIPN severity each fall within the same low-scoring category and very few patients receive the highest score.

To illustrate another grading scale limitation, consider how several different oncology providers might define moderate, severe, and life-threatening neuropathy. Because no operational definitions are provided for the various grades, each provider may define these grades differently, leading to lack of consistency and poor reliability across providers.

Based on these examples, it is easy to see why grading scales are problematic. However, grading scale use is deeply embedded within clinical and research practice. Mounting evidence supports the stance that grading scales should no longer be used or, at the very least, should be used alongside other patient-reported outcome measures (Atkinson et al., 2011; Basch et al., 2009; Kuroi et al., 2009; Shimozuma et al., 2009; Sloan et al., 2007). Shimozuma et al. (2009) compared several validated patient-reported outcome measure scores with provider-obtained NCI CTCAE scores and found that TIPN was consistently reported to be more prevalent and severe when quantified using patient-reported outcome measures. In another large cooperative group study in which 696 patients received oxaliplatin for colorectal cancer, neuropathy was quantified using both the NCI CTCAE and a patient-reported numeric rating scale (NRS) (Goldberg et al., 2004). In that study, neuropathy onset was detected several months sooner when the NRS was used versus the NCI CTCAE, allowing timelier oxaliplatin dose modifications (Morton et al., 2005; Sloan et al., 2007). This evidence supports the position that patient-reported outcome measures should be integrated into clinical trials because grading scales alone do not adequately quantify dose-limiting adverse events.

Table 2 provides a summary of selected TIPN measures that have been tested in patients receiving taxanes. In addition, two reviews (Cavaletti et al., 2010; Griffith et al., 2010) have

TABLE 2. Peripheral Neuropathy Measurement Tools Tested in Patients Receiving Taxanes

Measure	Type	Sample	Description
Tools			
Chemotherapy-Induced Peripheral Neuropathy Tool (Tofthagen et al., 2011)	Subjective; patient reported	Mixed population of patients with cancer and neurotoxic agents	The Chemotherapy-Induced Peripheral Neuropathy Tool is a 50-item self-report questionnaire that measures interference with daily activities (14 items) and the presence, severity, distress, and frequency of nine peripheral neuropathy symptoms (cold sensitivity, muscle and joint aches, numbness and tingling in hands and feet, loss of balance, weakness, and nerve pain) based on an 11-point scale (36 items). Satisfactory reliability and validity have been demonstrated; sensitivity to change and clinical use have not been evaluated. The length of this instrument makes it less feasible for use in busy clinical settings.
FACT/GOG-Ntx subscale (Calhoun et al., 2003; Cavaletti et al., 2010; Griffith et al., 2010; Huang et al., 2007)	Subjective; patient reported	Patients with cancer receiving carboplatin and paclitaxel	The FACT/GOG-Ntx is an 11-item neurotoxicity subscale of the FACT-General scale, assessing sensory, motor, and auditory function. Items are scored from 0 (not at all) to 4 (very much). Hand and feet symptoms are assessed separately, a potential advantage of this instrument. One weakness is that the two auditory items are not relevant to TIPN. Satisfactory reliability and validity have been demonstrated. The FACT/GOG-Ntx is short and can be easily administered to patients by nurses working in busy clinical settings.
Patient Neurotoxicity Questionnaire (Shimozuma et al., 2009)	Subjective; patient reported	Patients with cancer receiving taxanes	Contains two subjective items that assess sensory and motor neuropathy, which are graded from A (no neuropathy) to E (severe neuropathy). Interference with daily activities is used to differentiate between mild versus moderately severe and severe symptoms. Hand and feet symptoms are assessed together, a potential limitation of the measure. The terms "mild" and "moderate" are not linked with operational definitions, potentially leading to suboptimal reliability. As such, satisfactory validity has been demonstrated, but reliability data are not available. Interpretation of a numeric versus alphabetic rating scale may be more intuitive for patients and clinicians. This measure would be easy for nurses to administer to patients, but instrument reliability should be tested before being mainstreamed into clinical practice.
Peripheral Neuropathy Scale (Almadrones et al., 2004)	Subjective; patient reported	Patients with cancer receiving cisplatin and paclitaxel	The Peripheral Neuropathy Scale is a tool that combines an eight-item functional status scale with an 11-item neuropathy scale. Items from the scale were later revised and became the basis for the FACT/GOG-Ntx subscale.
QLQ-CIPN20 (Postma et al., 2005)	Subjective; patient reported	Mixed population of patients with cancer and neurotoxic agents	The QLQ-CIPN20 is a 20-item self-report questionnaire designed to supplement the EORTC quality-of-life questionnaire. The QLQ-CIPN20 contains nine items that assess sensory function, eight items that assess motor function, and three items that assess autonomic function. The extent to which patients experience neuropathy symptoms and associated functional limitations are scored from 1 (not at all) to 4 (very much). Hand and feet symptoms are assessed separately, a potential advantage of this instrument. Only internal consistency reliability testing has been reported. Additional psychometric testing is warranted before this instrument can be used in routine practice.
TNS (full) (Cavaletti et al., 2006, 2010; Chaudhry et al., 1994; Cornblath et al., 1999; Griffith et al., 2010; Smith et al., 2008)	Subjective/objective; provider reported based on history and physical examination	Mixed population of patients with cancer receiving neurotoxic agents	The TNS is a composite instrument that facilitates objective scoring of peripheral neuropathy signs and symptoms. Items include pinprick sensation; vibration sensation using a 128 Hz tuning fork; quantitative sensory testing of vibration and temperature sensation; sensory and motor nerve conduction study findings; tendon reflexes; strength; patient-reported numbness, tingling, and neuropathic pain distal to proximal extension; and motor and autonomic symptoms. All items are scored from 0 (no neuropathy) to 4 (severe neuropathy). Item scores are added together to comprise a total score. Satisfactory reliability and validity have been demonstrated.
TNS (shortened version) (Griffith et al., 2010; Lavoie Smith et al., 2011; Smith et al., 2010)	Subjective/objective; provider reported based on history and physical examination	Patients with cancer receiving taxanes and platinums	The shortened TNS includes the following items: patient-reported numbness, tingling, and neuropathic pain distal to proximal extension; vibration sensation using a 128-Hz tuning fork; and tendon reflexes. All items are scored from 0 (no neuropathy) to 4 (severe neuropathy). Item scores are added together to comprise a total score. Satisfactory reliability and validity have been demonstrated, and assessments can be obtained by nurses in about five minutes.

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ECOG—Eastern Cooperative Oncology Group; EORTC—European Organisation for the Research and Treatment of Cancer; FACT/GOG-Ntx—Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity; NCI CTCAE—National Cancer Institute's Common Terminology Criteria for Adverse Events; QLQ-CIPN20—Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy 20; TIPN—taxane-induced peripheral neuropathy; TNS—Total Neuropathy Score; WHO—World Health Organization

TABLE 2. Peripheral Neuropathy Measurement Tools Tested in Patients Receiving Taxanes *(Continued)*

Measure	Type	Sample	Description
Grading Scales			
NCI CTCAE, ECOG, Ajani, WHO (Cavaletti et al., 2010; Griffith et al., 2010; Postma et al., 1998)	Clinician reported	Mixed population of patients with cancer receiving neurotoxic agents	The scales guide gross assessment of neurotoxicity through a combination of subjective and objective parameters. Toxicity is graded from 0–4/5, with higher numbers representing worse neuropathy. The scoring criteria used in the various grading scales and versions are not consistent across scales. Terms such as "mild," "moderate," and "severe" are used without commonly accepted definitions. Grading-scale floor effects and suboptimal reliability, validity, and sensitivity have been reported.

ECOG—Eastern Cooperative Oncology Group; EORTC—European Organisation for the Research and Treatment of Cancer; FACT/GOG-Ntx—Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity; NCI CTCAE—National Cancer Institute's Common Terminology Criteria for Adverse Events; QLQ-CIPN20—Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy 20; TIPN—taxane-induced peripheral neuropathy; TNS—Total Neuropathy Score; WHO—World Health Organization

summarized the available literature regarding the development of instruments to measure chemotherapy-induced peripheral neuropathy. Griffith et al. (2010) used a meticulous process to identify and evaluate published research and recommended two measures for future use: the FACT/GOG-Ntx (Calhoun et al., 2003) and a shortened version of the TNS (Chaudhry et al., 1994; Cornblath et al., 1999; Griffith et al., 2010; Lavoie Smith et al., 2011; Smith et al., 2010). Several advantages in routinely assessing TIPN using those two measures exist. First, the measures have undergone more extensive testing in patients with TIPN compared with other measures and have been shown to have strong psychometric properties. This combined subjective/objective measurement approach will enhance the understanding of TIPN prevalence and severity because subtle differences in TIPN will be more detectable and patients (not physicians or nurses) will have an opportunity to describe their symptoms and related functional limitations.

In addition to being reliable and valid, the FACT/GOG-Ntx and the shortened TNS instruments are relatively easy to use. The FACT/GOG-Ntx subscale consists of only 11 items and can be given to patients to complete while they wait to receive each taxane treatment. The form is written at a sixth-grade reading level and takes only a few minutes to complete (Calhoun et al., 2003). Table 3 provides information regarding the TNS scoring criteria (modified). Clinicians would likely need to keep these criteria nearby; however, this should not be a barrier to its use because many clinicians also need to frequently refer to the NCI CTCAE scoring criteria when grading neuropathy and a variety of other adverse events. The shortened TNS has been shown to be feasible for use by advanced practice nurses, and an ongoing study has demonstrated that staff nurses are capable of using the TNS when measuring vincristine-induced neuropathy in children with leukemia (Smith, Renbarger, et al., 2012). With the shortened version, a TNS-based assessment can be completed in about five minutes. Subjective numbness, tingling, and neuropathic pain scores are obtained by asking the patient to describe the distal to proximal extension of these symptoms. For example, a nurse would ask the patient whether his or her symptoms are present only in the toes or if they extend further up the foot to the ankle and beyond. More severe TIPN is associated with greater proximal extension of symptoms. Hand symptoms typically appear after feet symptoms have already

TABLE 3. Shortened and Revised Total Neuropathy Scoring Criteria

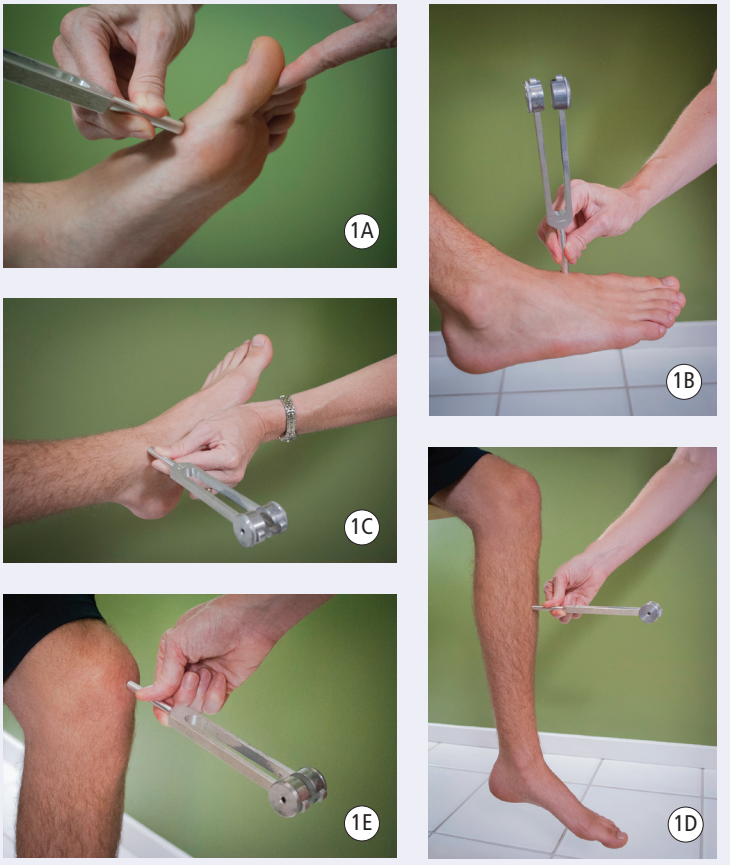
Item	0	1	2	3	4
Symptom extension (tingling)	None	Symptoms from toes to midfoot (not including heel)	Symptoms from midfoot to ankle	Symptoms extend above ankle to knee without upper extremity symptoms	Symptoms above knee or concurrent lower and upper extremity symptoms
Symptom extension (numbness)	None	Symptoms from toes to midfoot (not including heel)	Symptoms from midfoot to ankle	Symptoms extend above ankle to knee without upper extremity symptoms	Symptoms above knee or concurrent lower and upper extremity symptoms
Symptom extension (neuropathic pain)	None	Symptoms from toes to midfoot (not including heel)	Symptoms from midfoot to ankle	Symptoms extend above ankle to knee without upper extremity symptoms	Symptoms above knee or concurrent lower and upper extremity symptoms
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent or others reduced	All reflexes absent
Vibration sensibility	Normal	Absent or decreased from toes to midfoot (not including heel)	Absent or decreased from midfoot to ankle	Absent or decreased above ankle to knee	Absent or decreased above knee or in lower and upper extremities concurrently

Note. Based on information from Chaudhry et al., 1994; Cornblath et al., 1999; Lavoie Smith et al., 2011; Smith et al., 2008, 2010.

developed because the upper extremity nerve fibers are more proximal to the spinal cord. One limitation of the TNS scoring criteria is that symptom severity cannot be adequately assessed. Therefore, use of a 0–10 NRS should be considered, particularly when assessing neuropathic pain severity (Lavoie Smith et al., 2009; Smith et al., 2008).

The most difficult aspect of performing the TNS-based assessment is learning how to obtain tendon reflex scores; however, if nurses need assistance, they can seek it from an experienced nurse practitioner or physician colleagues. Reflex assessment provides a measure of both motor and sensory function. The Achilles reflex should be tested first; if the reflex is diminished or absent, other reflexes should be assessed, such as patellar, brachioradialis, bicep, and tricep. However, if the Achilles reflex is normal, no additional reflex testing is needed. If asymmetrical findings are discovered (for any TNS item), the most severe finding is used for scoring.

Gaining competence in assessing vibration sensibility testing using a basic 128 Hz weighted tuning fork is not difficult, and nurses and patients seem to enjoy conducting and undergoing these assessments, respectively. The tuning fork should be firmly tapped on the palm of the hand to initiate vibration. The vibrating tuning fork is first placed on the interphalangeal joint of the great toe (see Figure 1A). The nurse places a finger under the patient's toe to compare the patient's vibration sensibility with the nurse's (control). The nurse should feel the vibration through the patient's toe for at least as long as the patient. The patient is instructed to report when vibration is no longer detected. If the patient feels the vibration longer than the nurse, this is defined as normal. If vibration sensation is normal at the great toe, it will be normal elsewhere (more proximally), and additional assessments are not needed. However, if vibration sensation is diminished or absent in the great toe, the nurse then conducts the testing at the middorsal foot and medial malleolus (ankle) areas (see Figures 1B and 1C), followed by the midfibular and patellar regions (see Figures 1D and 1E). Upper extremity vibration sensibility is first tested at the distal interphalangeal joint of the index finger (see Figure 2A) and then the ulnar styloid (wrist) (see Figure 2B) and lateral epicondyle (elbow) (see Figure 2C). Once the patient is no longer able to sense vibration, the nurse determines whether vibration was still detectable by quickly moving the tuning fork to his or her own ankle, knee, or wrist. However, one limitation is that nurses with impaired vibration sensation are less able to obtain valid scores. An alternative approach is to record how long (in seconds) the patient feels the vibration. Feeling the vibration for about 15 seconds is considered to be normal for all testing locations except for the patella (10 seconds) and index finger (25 seconds) (Ohsumi & Sunada, 2004). Variability will exist based on how hard the tuning fork is tapped. A specialized tuning fork (Rydel-Seiffer) is available to facilitate vibration assessment, but these generally are not available in oncology clinical settings (Pestronk et al., 2004). Although this low-tech approach to vibration assessment is imperfect, it has been shown to be reliable, valid, and more sensitive to change over time than grading scale scoring (Lavoie Smith et al., 2011; Smith, Renbarger, et al., 2012).



Note. The tuning fork is firmly tapped on the palm and then placed on the interphalangeal joint of the great toe (1A). If vibration sensation is diminished or absent in the great toe, testing should be performed at the middorsal foot (1B) and the medial malleolus (1C), followed by the midfibular (1D) and patellar (1E) regions.

FIGURE 1. Performing a Vibration Sensibility Test of the Lower Extremities

Note. Photos courtesy of Josh Weiland Photography. Used with permission.

Treating Taxane-Induced Peripheral Neuropathy

Despite escalating attempts to find effective treatments for TIPN, little progress has been made (Pachman, Barton, Watson, & Loprinzi, 2011; Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007; Wolf, Barton, Kottschade, Grothey, & Loprinzi, 2008). Ineffective drugs for treating TIPN include amitriptyline (Kautio et al., 2009), gabapentin (Rao et al., 2007), and lamotrigine (Rao et al., 2008). Barton et al. (2011) tested the efficacy of topical baclofen, amitriptyline, and ketamine (BAK) gel. The researchers reported that BAK was only marginally effective, possibly because of subtherapeutic dosing. One phase III trial testing the efficacy of acetyl-L-carnitine revealed unexpected findings in that the drug worsened TIPN symptoms compared with placebo (Hershman et al., 2012). Positive findings came from a large, phase III placebo-controlled study conducted by

the Cancer and Leukemia Group B, which demonstrated that oral duloxetine 60 mg daily was effective in diminishing taxane-related painful neuropathy (Smith, Pang, et al., 2012). With only one positive phase III trial to date, continued research examining new interventions to prevent or diminish TIPN is needed.

Nurses can play a role in diminishing some of the negative consequences of TIPN by educating patients on the importance of reporting symptoms. By encouraging patients to report their symptoms and taking a more active role in TIPN assessment, nurses can help ensure that taxane treatment is modified sooner. Impaired foot and hand sensation places patients at increased risk for mechanical or thermal injury. Nurses should counsel patients regarding strategies to minimize injury risk. Such strategies include turning down the temperature settings on home water heaters, using gloves when washing dishes or gardening, and always wearing shoes with soles, particularly when outdoors. Tofthagen, Overcash, and Kip (2012) reported that patients receiving taxanes may be more likely to fall than those receiving platinums, and that a higher cumulative chemotherapy dose, impaired balance, muscle weakness, more severe TIPN symptoms, and impaired walking and driving ability are predictive of increased fall risk. Nurses should advise patients who are at high risk for tripping or falling to remove clutter and scatter rugs in their homes. Because patients with TIPN need to rely more heavily on visual clues when monitoring the location of their feet on the ground, patients should avoid walking in poorly lighted areas. A referral to an occupational or physical therapist may be necessary in cases of severely impaired balance, foot drop, or extremity weakness. Adaptive equipment, such as large-handled eating utensils, foot braces, walkers, or canes can be helpful to optimize functional capacity and safety. In addition, muscle-strengthening exercises may help to minimize weakness. Patients with severely impaired plantar foot sensation or foot drop should be advised not to drive. Lastly, because orthostatic hypotension can occur because of autonomic neuropathy, nurses should teach patients to change positions slowly so as to avoid syncopal episodes.

Future Research

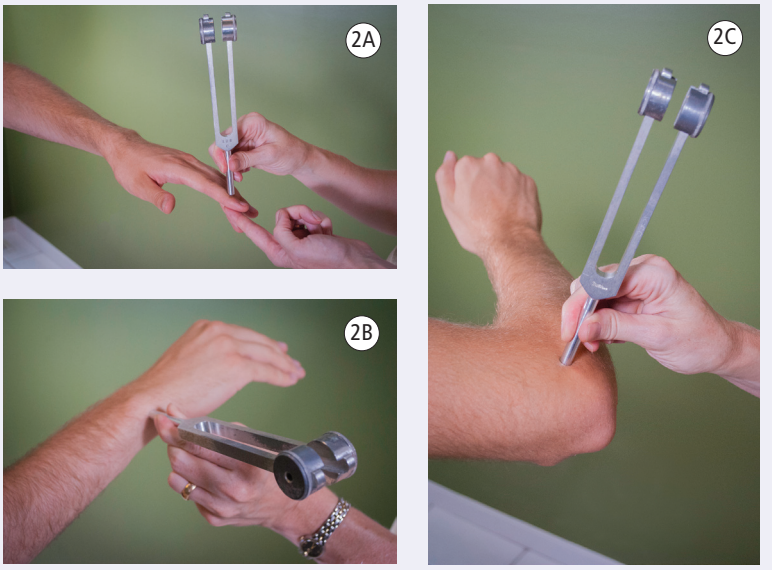
Studies are beginning to suggest that taxane neurotoxicity may be directly related to individual variations in neurotoxic drug metabolism, distribution, and elimination; however, the results, to date, are inconclusive (Bergmann et al., 2011; Sissung et al., 2006). Three large studies have identified genetic polymorphisms associated with TIPN (Hertz et al., 2012; Kroetz et al., 2010; Schneider et al., 2011). If detection of genetic predictors becomes the standard of care, this could lead to a significant paradigm shift in how TIPN is managed. Patients determined to be at high risk via a genetic test performed prior to receiving taxane therapy might be offered alternative treatments or altered dosing schedules. As one example, it may be possible to individualize taxane dosing so that those with genetic polymorphisms leading to more efficient taxane metabolism would receive higher doses, whereas slow metabolizers would receive lower doses. That approach could ultimately result in improved taxane efficacy while minimizing severe and disabling peripheral neuropathy for long-term cancer survivors.

Implications for Practice

- Taxane-induced peripheral neuropathy should be quantified by determination of the distal to proximal extension of numbness, tingling, and neuropathic pain, as well as vibration sensibility and tendon reflexes.
- Neuropathic pain severity should be assessed using a 0–10 numeric rating scale.
- Validated assessment tools should be administered to patients prior to each taxane treatment.

Conclusion

TIPN is an underrecognized problem that significantly compromises quality of life for patients with breast cancer. TIPN is underrecognized because of continued reliance on suboptimal assessment approaches. Emerging empirical evidence suggests that more reliable, valid, sensitive, and clinically feasible TIPN measurement approaches should be used to quantify TIPN in clinical and research settings. However, implementing practice change based on this evidence continues to be challenging. This article provides practical suggestions for how nurses can take the lead in improving TIPN measurement practices. In addition, the search must continue for effective interventions that will ameliorate or even prevent distressing and disabling TIPN symptoms for breast cancer survivors receiving taxane therapy.



Note. The tuning fork is firmly tapped on the palm and then placed at the distal interphalangeal joint of the index finger (2A), the ulnar styloid (2B), and the lateral epicondyle (2C).

FIGURE 2. Performing a Vibration Sensibility Test of the Upper Extremities

Note. Photos courtesy of Josh Weiland Photography. Used with permission.

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