



MEASURING ONCOLOGY NURSING-SENSITIVE PATIENT OUTCOMES: EVIDENCE-BASED SUMMARY

1. **Outcome:** Chemotherapy-induced peripheral neuropathy
2. **Category:** Symptom experience
3. **Definitions:**

Peripheral neuropathy is a dysfunction of peripheral, motor, sensory, and autonomic neurons resulting in peripheral neuropathic signs and symptoms (Postma & Heimans, 2000). **Chemotherapy-induced peripheral neuropathy** is hypothesized to occur as the end result of neurotoxic chemotherapy and biotherapy agents directly damaging nerve fibers by inactivating the components required to maintain the metabolic needs of the axon. The longer and larger distal axons are affected first and result in interruptions of axonal transport and degeneration of myelinated nerve fibers and unmyelinated axons.

Peripheral neuropathy is the end result of primarily distal motor and sensory deficits. Motor neuron involvement appears as lower-extremity muscle wasting accompanied by sensations of weakness that typically begin in the distal lower extremities and spread in a proximal fashion. Visceral motor nerve cells of the autonomic nervous system that are responsible for the transmission of impulses to smooth muscle and glands also can be affected.

ICD-10 Criteria for Peripheral Neuropathy

Diagnostic criteria related to cancer and cancer treatment-induced peripheral neuropathy are lacking. Peripheral neuropathy is coded under ICD-10 *Diabetes Mellitus*.

ICD-9 357.6 Polyneuropathy due to drugs

Reference for Definitions:

Postma, T., & Heimans, J. (2000). Grading of chemotherapy-induced peripheral neuropathy. *Annals of Oncology*, 11, 509–513.



4. Integrative Reviews (in this emerging field, no meta-analyses are available)

Reviews Related to Assessment and Measurement of Peripheral Neuropathy

Armstrong, T. Almadrones, L. & Gilbert, M. (2005). Chemotherapy-induced Peripheral neuropathy. *Oncology Nursing Forum*, 32(2), 305-311. "ONS Member Access" link to <http://www.ons.org/publications/journals/ONF>

Corbo, M., & Balmaceda, C. (2001). Peripheral neuropathy in cancer patients. *Cancer Investigation*, 19, 369–382. [PubMed Abstract](#)

Dellon, A.L. (1993). A numerical grading scale for peripheral nerve function. *Journal of Hand Therapy*, 6, 152–160. [PubMed Abstract](#)

McDougall, A., & McLeod, J. (1996). Autonomic neuropathy, I: Clinical features, investigation, pathophysiology, and treatment. *Journal of the Neurological Sciences*, 137(2), 79–88. [PubMed Abstract](#)

McDougall, A., & McLeod, J. (1996). Autonomic neuropathy, II: Specific peripheral neuropathies. *Journal of the Neurological Sciences*, 138(1–2), 1–13. [PubMed Abstract](#)

Ocean, A., & Vahdat, L. (2004). Chemotherapy-induced peripheral neuropathy: Pathogenesis and emerging therapies. *Supportive Care in Cancer*, 12, 619–625. [PubMed Abstract](#)

Postma, T., & Heimans, J. (2000). Grading of chemotherapy-induced peripheral neuropathy. *Annals of Oncology*, 11, 509–513. [PubMed Abstract](#)

Postma, T., Heimans, J., Muller, M., Ossenkopple, G., Vermorken, J., & Aronson, N. (1998). Pitfalls in grading severity of chemotherapy induced peripheral neuropathy. *Annals of Oncology*, 9, 739–744. [PubMed Abstract](#)

Quasthoff, S., & Hartung, H.P. (2002). Chemotherapy-induced peripheral neuropathy. *Journal of Neurology*, 249, 9 17. [PubMed Abstract](#)

Tobin, K., Giuliani, M., & Lacomis, D. (1999). Comparison of different modalities for the detection of small fiber neuropathy. *Clinical Neurophysiology*, 110, 1909–1912. [PubMed Abstract](#)

Verstappen, C., Heimans, J. Hoekman, K., & Postma, T. (2003). Neurotoxic complications of chemotherapy in patients with cancer: Clinical signs and optimal management. *Drugs*, 63,1549–1563. [PubMed Abstract](#)

Visovsky, C. (2003). Chemotherapy-induced peripheral neuropathy. *Cancer Investigation*, 21, 439–451. [PubMed Abstract](#)

Reviews With Abstracts Related to the Measurement or Grading of Chemotherapy-Induced Peripheral Neuropathy

Dellon, A.L. (1993). A numerical grading scale for peripheral nerve function. *Journal of Hand Therapy*, 6, 152–160. [PubMed Abstract](#)



- Postma, T., & Heimans, J. (2000). Grading of chemotherapy-induced peripheral neuropathy. *Annals of Oncology*, 11, 509–513. [PubMed Abstract](#)
- Tobin, K., Giulani, M., & Lacomis, D. (1999). Comparison of different modalities for the detection of small fiber neuropathy. *Clinical Neurophysiology*, 110, 1909–1912. [PubMed Abstract](#)
- Visovsky, C. (2003). Chemotherapy-induced peripheral neuropathy. *Cancer Investigation*, 21, 439–451. [PubMed Abstract](#)

Reviews Related to Management of Peripheral Neuropathy

Few systematic reviews are related to this topic. This list includes reviews of prevention and management approaches to peripheral neuropathy as well as management of pain related to neuropathy. This includes reviews published in textbooks.

- Armstrong, T. Almadrones, L. & Gilbert, M. (2005). Chemotherapy-induced peripheral neuropathy. *Oncology Nursing Forum*, 32(2), 305-311. “ONS Member Access” link to <http://www.ons.org/publications/journals/ONF>
- Corbo, M., & Balmaceda, C. (2001). Peripheral neuropathy in cancer patients. *Cancer Investigation*, 19, 369–382. [PubMed Abstract](#)
- Hartmann, J., Kollmannsberger, C., Lanz, L., & Bokemeyer, C. (1999). Platinum organ toxicity and possible prevention in patients with testicular cancer. *International Journal of Cancer*, 83, 866–869. [PubMed Abstract](#)
- Kanner, R. (2001). Diagnosis and management of neuropathic pain in patients with cancer. *Cancer Investigation*, 19, 324–333. [PubMed Abstract](#)
- Markman, M. (2004). Can we do a better job of preventing clinically-relevant peripheral neuropathy resulting from carboplatin/paclitaxel chemotherapy? *Cancer Investigation*, 22, 471–473. [PubMed Abstract](#)
- Ocean, A., & Vahdat, L. (2004). Chemotherapy-induced peripheral neuropathy: Pathogenesis and emerging therapies. *Supportive Care in Cancer*, 12, 619–625. [PubMed Abstract](#)
- Paulson, L., & Kilmer, D. (2001). Orthotic management in peripheral neuropathy. *Physical Medicine and Rehabilitation Clinics of North America*, 12, 433–445. [PubMed Abstract](#)
- Yuen, E. (2001). The role of neurotrophic factors in disorders of peripheral nerves and motor neurons. *Physical Medicine and Rehabilitation Clinics of North America*, 12, 293–306. [PubMed Abstract](#)



5. Guidelines and Standards

Currently, no guidelines or standards exist for the assessment or management of chemotherapy-induced peripheral neuropathy. The American Society of Clinical Oncology (ASCO) (1999) clinical practice guidelines for the use of chemotherapy and radioprotectants provide evidence related to the prevention of chemotherapy-induced neurotoxicities and can be found at www.asco.org (also see *Pharmacologic Interventions* below).

Peripheral Neuropathy

Monitoring Parameter(s)

- Perform subjective and objective assessment of symptoms related to peripheral neuropathy: pain, numbness, burning, tingling, paresthesias, and ability to perform fine motor skills.
- Perform objective assessment of symptoms related to peripheral neuropathy: deep tendon reflexes, vibration sensation, touch, proprioception, muscle strength, cranial nerve assessment (particularly vision and hearing), orthostatic blood pressure measurement, and Lhermitte's sign.
- Assess for the presence of factors related to peripheral neuropathy: neuropathic pain syndromes and depression.
- Assess for motor neuron-related signs of neuropathy: muscle weakness and atrophy, hypotonia, hyporeflexia, or areflexia.
- Assess for sensory neuron-related signs of neuropathy: burning pain, paresthesias, and dysesthesias, including loss of proprioception, ataxia, loss of balance, and a decrease in vibration sensation.
- Assess for signs of autonomic dysfunction related to peripheral neuropathy: constipation, paralytic ileus, and urinary retention, orthostatic blood pressure alterations, sexual dysfunction.
- Assess for the presence of preexisting neuropathies related to other illnesses or disease states: diabetes, human immunodeficiency virus, alcoholism, and hereditary conditions (e.g., Charcot Marie Tooth Disease).
- Quantitative tests: Quantitative Sensory Testing (QST) nerve conduction studies, electromyograms and sural nerve biopsy may be preformed for diagnostic purposes or as correlates to clinical symptoms. Little data supports the routine use of quantitative testing to make a confirmatory diagnosis of chemotherapy-induced peripheral neuropathy because the diagnosis is typically made by clinical presentation. The use of QST in determining the presence of diabetic neuropathy is increasing, as it provides information concerning large and small peripheral nerve fibers. The use of QST has been tested in few studies of chemotherapy-induced neuropathy.



Intervention (s)

- *Exercise Therapy*
 - Few studies address the value of exercise for individuals with peripheral neuropathy.
 - Performing passive range of motion exercises enhances reinnervation in denervated muscle and appears to have therapeutic value.
 - Some evidence suggests that resistance exercises may be of benefit in increasing strength for individuals weakened by neuropathy.
 - Refer clients to a physical therapist for orthotic braces or a splint to assist with lower-extremity alignment and balance.
 - Exercise therapy must take into consideration safety issues in regard to peripheral neuropathy. Loss of sensation and muscle weakness in the lower extremities limit patients' abilities to sense changes in terrain, predisposing them to falls.

- *Occupational Therapy*
 - The individual with an occupation requiring fast-paced mobility may require vocational counseling.
 - Assesses clients' capabilities to perform self-care activities and recommend assistive devices as needed.

- *Educational Interventions*
 - Teach clients strategies for managing personal safety, such as using visual input to compensate for loss of lower-extremity sensation in navigating changing terrain.
 - Teach clients about the risk for ischemic or thermal injury resulting from loss of sensation in extremities.
 - Teach strategies for symptoms of autonomic dysfunction (postural hypotension, constipation, urinary retention), such as dangling the legs prior to arising and the use of a high-fiber diet, adequate fluid intake, and exercise.

- *Pharmacologic Interventions*
 - *Cytoprotective agents*, such as amifostine (Ethyol[®], ALZA Corporation, Mountain View, CA) has shown some efficacy in reducing the incidence and severity of the neurotoxicity experienced.

However, at this time, ASCO's Clinical Practice Guidelines (1999) concluded that insufficient data support the routine use of amifostine to prevent cisplatin or paclitaxel-induced neuropathy.

- o *Calcium and magnesium infusions* may hold promise in the prevention of oxaliplatinum -induced neurotoxicity. One study by Gamelin et al. (2004) has investigated the use of calcium gluconate and magnesium chloride infusions as a preventative approach to oxaliplatinum-induced neurotoxicity. Not enough evidence supports the routine use of calcium and magnesium infusions in the prevention of neuropathy. Currently, a prospective randomized multicenter, double blind, placebo controlled trial is underway to investigate this further (Gamelin et al., 2004).
- o *Glutamine*, an amino acid, has been proposed as a neuroprotective agent and as a mediator in the myalgia and arthralgias that accompany cisplatin, paclitaxel and vincristine therapy. Studies indicate that glutamine may offer a reduction in severity of neuropathy, especially with dose-intensive paclitaxel therapy. The manner in which glutamate offers neuroprotection is not yet known, and further trials are in progress.
- o *Glutathione* is a natural thiol tripeptide involved in protective mechanisms resulting from oxidative injury, and in the prevention of platinum accumulation in the dorsal root ganglia. Studies of using glutathione in the prevention of cisplatin-induced neuropathy have been inconsistent, and further studies are needed.
- o *Neurotrophic factors*, such as recombinant nerve growth factor (rhNGF), are currently in phase II and III clinical trials. Preliminary reports suggest that they have variable success, and more data will be needed before recommendations about use can be made.
- o *Pain control measures: Tramadol hydrochlorid* (Ultram[®], Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ), *tricyclic antidepressants*, and *gabapentin* (Neurontin[®], Pfizer Inc., New York, NY) have shown some degree of efficacy in the management of neuropathic pain. Additional trials are needed to confirm efficacy.
- o *Other agents*, such as ORG 2766 (a coricotropin analog), venlafaxine (Effexor[®], Wyeth Pharmaceuticals Inc., Madison, NJ), and acetyl-L carnitine also are being studied for their effectiveness in the prevention of chemotherapy-induced peripheral neuropathy, and trials are still in progress.

Comments. Depression can accompany neuropathic pain syndromes. Antidepressant agents can enhance the action of pain medication regimens in these cases.



6. Table(s) of Tools to Measure Oncology Nursing-Sensitive Outcome: Peripheral Neuropathy

This table includes tools specifically designed to assess and measure chemotherapy-induced peripheral neuropathy that have been used in patients with cancer.

**Table 6A. Description of Tools
Tools for Grading Neuropathy: Toxicity Grading Scales**

Name of Tool	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
World Health Organization Toxicity Criteria Miller et al., 1981	None	Paresthesias and/or decreased deep tendon reflexes	Severe paresthesias and/or mild weakness Mild weakness	Intolerable paresthesias and/or motor loss	Paralysis
Eastern Cooperative Oncology Group	None	Decreased deep tendon reflexes Mild paresthesias Mild constipation	Absent deep tendon reflexes Severe constipation Mild weakness	Disabling sensory loss, severe peripheral neuropathic pain, obstipation, severe weakness, bladder dysfunction	Respiratory dysfunction secondary to weakness, obstipation requiring surgery, paralysis confining patient to bed or wheelchair
National Cancer Institute of Canada Common Toxicity Criteria* Sensory Neuropathy	None	Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Objective sensory loss or paresthesia, interfering with function, but not interfering with activities of daily living (ADL)	Sensory loss or paresthesia interfering with ADL	Permanent sensory loss that interferes with function
Motor Neuropathy	None	Subjective weakness but no objective findings	Objective mild weakness, interfering with function but not interfering with ADL	Severe paresthesia, moderate objective abnormality, severe functional abnormality	Paralysis



Name of Tool	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
<p>Ajani Motor Neuropathy Ajani, 1990</p> <p>Sensory Neuropathy</p> <p>Motor Neuropathy</p>	<p>None</p> <p>None</p>	<p>Paresthesia and decreased deep tendon reflexes</p> <p>Mild transient muscle weakness</p>	<p>Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional abnormality</p> <p>Persistent moderate weakness, but ambulatory</p>	<p>Severe paresthesia, moderate objective, severe functional abnormality</p> <p>Unable to ambulate</p>	<p>Complete sensory loss, loss of function</p> <p>Complete paralysis</p>
<p>Total Neuropathy Scale</p> <p>Sensory Symptoms</p> <p>Motor Symptoms</p> <p>Pin Sensibility</p> <p>Vibration Sensibility</p> <p>Reflexes</p>	<p>None</p> <p>None</p> <p>None</p> <p>None</p> <p>None</p>	<p>Limited to fingers or toes</p> <p>Slight difficulty</p> <p>Reduced in fingers and toes</p> <p>Reduced in fingers and toes</p> <p>Reduced ankle reflex</p>	<p>Extension to ankle or wrist</p> <p>Moderate difficulty</p> <p>Reduced to ankle</p> <p>Moderate difficulty Reduced to ankle</p> <p>Absent ankle reflex</p>	<p>Extension to knee or elbow</p> <p>Requires assistance</p> <p>Reduced to elbow or knee</p> <p>Reduced to elbow or knee</p> <p>All reflexes reduced</p>	<p>Extension to above the knee or elbow, functionally disabling</p> <p>Functionally disabling</p> <p>Reduced above elbow or knee</p> <p>Reduced above elbow or knee</p> <p>All reflexes absent</p>



Name of Tool	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Total Neuropathy Scale (Continued)					
Autonomic symptoms	None	1	2	3	4 or 5
Vibration sensation	Normal–125	126–150	151–200	201–300	> 300
Sural amplitude	Normal or reduced < 5%	76%–96%	51%–75%	26%–50%	0%–25%
Peroneal amplitude	Normal or reduced < 5%	76%–96%	51%–75%	26%–50%	0–25%
National Cancer Institute, Common Terminology Criteria for Adverse Events					
Neuropathy cranial	None	Asymptomatic, detected on examination or testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life threatening, disabling
Neuropathy motor	None	Asymptomatic, weakness detected on exam or testing only	Symptomatic weakness, interfering with function, but not interfering with ADL	Weakness interfering with ADL, bracing or Assistance to walk indicated	Life threatening, disabling
Neuropathy sensory	None	Asymptomatic, loss of deep tendon reflexes, paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling) interfering with function but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling

* The National Cancer Institute's Common Terminology Criteria for Adverse Events has a grade 5 toxicity category for all neuropathy items: death.



Table 6B. Description of Tools

Tools to Measure Oncology Nursing-Sensitive Outcome: Peripheral Neuropathy

The FACT tools are available online at no charge at www.facit.org. However, there is an additional charge for the tool psychometrics, administration and scoring instructions.

Name of Tool	Author and Year	Domains or Factors	# of Items	Scaling	Scoring	Language	Comments
Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx)	Calhoun et al., 2000, 2003	Physical well-being Social well-being Emotional well-being Functional well-being Additional concerns (related to neuropathy)	7 7 6 7 11	0-4 not at all- very much	Scoring available at www.facit.org for additional charge	English Many other language translations of this tool are available	Two groups of women with ovarian cancer completed the FACT/GOG-Ntx. One group (A) was chemotherapy-naive with newly diagnosed ovarian cancer and a second group (B) with known neurotoxicities. Cronbach's alpha ranged from 0.84-0.90 for the 38-item FACT/GOG-Ntx total and from 0.71-0.88 for the individual subscales with the exception of Social Well-Being subscale (0.51-0.53) due to the fact that many patients chose not to answer the satisfaction with sexual activity question. Validity was determined by criterion-related and concurrent validity. The FACT/GOG-Ntx was able to differentiate between the patients with no neurotoxicity (Group A) and those with known chemotherapy-induced neuropathy (Group B). The separation of these two clinically distinct groups was > one standard deviation for over 6 months. Correlation coefficients for objective and subjective measures of neuropathy find sensory rating ($r = 0.19$ -



Name of Tool	Author and Year	Domains or Factors	# of Items	Scaling	Scoring	Language	Comments
FACT/GOG-Ntx (Continued)							0.73), motor ($r = 0.20-0.64$), and autonomic ($r = 0.03-0.49$) to have significant relationship to the Ntx subscale over time. Strength and reflexes revealed a moderate association with the Ntx subscale and Quantitative Sensory Testing (QST) showed a less degree of association over time.
Functional Assessment of Cancer Therapy – Taxane (Version 4)	Cella et al., 2003	Physical well-being Social well-being Emotional well-being Functional well-being Additional concerns	7 7 6 7 16	0–4 not at all– very much	Scoring available at www.facit.org for additional charge	English Many other language translations of this tool are available	FACT-Taxane: Cronbach's alpha for the 16-item taxane subscale ranged from 0.84-0.88. Criterion-related validity was determined for responsiveness to expected change by comparison of the FACT-Taxane with Karnofsky performance status in a sample of lung cancer patients receiving taxanes. There were no significant differences at baseline (prechemotherapy); however, significant group differences were observed at 6 and 12 weeks by decreases in scores from baseline indicating measurable neurotoxicity.
Peripheral Neuropathy Scale	Almadrones et al., 2004	Peripheral neuropathy	11	1–4 Not at all– very much	11 items are summed for a score of 11-44. Higher scores indicate higher degree of patient-	English	Cronbach's alpha (reliability) .91 for the 11-item PN scale. Construct validity was done using exploratory factor analysis with items 9,10, 13, 16, & 18 loading on Factor 1 (Hand Neuropathy) and items 11, 14, 17 & 19 loading onto Factor 2 (Foot Neuropathy). At T2, peripheral neuropathy was significantly associated



Name of Tool	Author and Year	Domains or Factors	# of Items	Scaling	Scoring	Language	Comments
Peripheral Neuropathy Scale (Continued)					reported peripheral neuropathy		with the Common Toxicity Criteria score, supporting the validity of the PNS.



7. References Related to Specific Instruments to Measure Peripheral Neuropathy

- Ajani, J.A., Welch, S.R., Raber, M.N., Fields, W.S., & Krakoff, I.H. (1990). Comprehensive criteria for assessing therapy-induced toxicity. *Cancer Investigation*, 8, 147–159
- Almadrones, L., McGuire, D., Walczak, J., Florio, C., & Chunqiao, T. (2004). Psychometric evaluation of two scales assessing functional status and peripheral neuropathy associated with chemotherapy for ovarian cancer: A Gynecologic Oncology Group study. *Oncology Nursing Forum*, 31, 615–623. “ONS Member Access” link to <http://www.ons.org/publications/journals/ONF>
- Brundage, M.D., Pater, J.L., & Zee, B. (1993). Assessing the reliability of two toxicity scales: Implications for interpreting toxicity data. *Journal of the National Cancer Institute*, 85, 1138–1148.
- Calhoun, E.A., Welshman, E.E., Chang, C.H., Lurain, J.R., Fishman, D.A., Hunt, T., & 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, 741-8.
- Calhoun, E.A., Fishman, D.A., Roland, P.Y., Lurain, J.R., Chang, C.H., & Cella, D. (2000). Validity and selective sensitivity of the FACT/GOG-Ntx. *Proceedings of the American Society of Clinical Oncology*, 19, 446a.
- Cavaletti, G., Bogliun, G., Marzorati, L., Zincone, A., Piatti, M., Colombo, N., et al. (2003). Grading of chemotherapy induced peripheral neurotoxicity using the Total Neuropathy Scale. *Neurology*, 61, 1297–1300.
- Cella, D., Peterman, A., Hudgens, S., Webster, K., & Socinski, M.A. (2003). Measuring the side effects of taxane therapy in oncology: The Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane). *Cancer*, 98, 822-31.
- Miller, A.B., Hoogstraten, B., Staquet, M., & Winkler, A. (1981). Reporting results of cancer treatment. *Cancer*, 47, 207-214.
- National Cancer Institute. (2003). *Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0*. U.S. Department of Health and Human Services: National Cancer Institute: Bethesda.
- Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T, et al. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology*, 5, 49–55.



8. Summary of Key Evidence That Nursing Interventions Influence This Outcome and Gaps in Current Evidence Base

This evidence is based on the integrated reviews and highlights evidence that nursing interventions influence peripheral neuropathy (Section 4). To date, no studies focus on cancer-related peripheral neuropathies in diverse populations.

A. Evidence That Nursing Interventions Influence Peripheral Neuropathy

- Careful physical assessment and monitoring of subjective peripheral neuropathy symptoms is important in the early detection of cancer-treatment related neurotoxicity.
- Passive range of motion and resistance exercises can enhance reinnervation and muscle strength.
- Routine nursing assessment of stance, gait and balance can identify individuals needing assistive devices such as orthotic braces. Some evidence suggests that such devices can improve lower extremity alignment and balance.
- Little evidence exists of the effectiveness of teaching interventions regarding issues of personal safety (ambulation strategies, thermal/ischemic injury risk, management of hypotension).
- Evidence is conflicting regarding the role and efficacy of cytoprotective agents, glutathione, glutamine, vitamin e supplementation, or neurotrophic factors in chemotherapy-induced peripheral neuropathy, and no evidence exists regarding nursing interventions for individuals receiving these emerging therapies.

B. Gaps in the Evidence

Prevalence and Pattern

- In describing peripheral neuropathies, distinguishing between motor, sensory, and autonomic symptoms becomes important. Most peripheral neuropathies demonstrate a mixture of motor and sensory signs.
- Assessment of symptom patterns based on different agents or combination regimens is lacking.
- Evidence surrounding the resolution of cancer therapy-induced peripheral neuropathy is conflicting, with some studies reporting resolution of neuropathy coinciding with the end of treatment and others reporting a more prolonged course.

Assessment and Measurement

- Classification systems of grading chemotherapy-induced peripheral neuropathy vary widely, and guidelines for their use is lacking.
- Most toxicity assessment scales use a combination of objective and subjective items in reporting neurotoxicity.



- Toxicity assessment scales have difficulty in distinguishing subtle differences between toxicity grades, making these differences difficult to delineate.
- The current system for grading chemotherapy-induced peripheral neuropathy lacks a mechanism to adequately follow changes in peripheral nerve function from baseline.
- Toxicity grading scales are lacking in their ability to determine the impact of neurological changes on the individual.
- Some important indicators of grading the neurotoxicity associated with chemotherapeutic agents, such as deep tendon reflexes, sensation, and motor function, are that these measures are, to some degree, dependent on the skill of the examiner. An inherent intra-subject variability in response and intra- or inter-rater variability in the estimation of these responses exist that must be controlled.
- Objective measures of neuropathy fail to capture the impact of peripheral neuropathy on the individual. The impact of peripheral neuropathy on quality of life has not been studied adequately.

Mechanisms/Etiology of Peripheral Neuropathy

- The mechanism of chemotherapy-induced peripheral neuropathy is not fully understood, and the type of injury to the peripheral nerves varies with the chemotherapeutic agent used and total accumulated dose. For example, neurotoxic agents can cause shrinkage and degeneration of the myelin sheath, reducing nerve conduction velocity. Antimitotic agents induce microtubule aggregation in the neurons and have been implicated in axonal atrophy and demyelination. The dorsal root ganglion and the organ of Corti are directly affected by the accumulation of cisplatin and the effects of its metabolites in those tissues, leading to a dose-dependent sensory polyneuropathy and subsequent tinnitus and high-frequency hearing loss. However, the exact mechanisms underlying these processes are not fully understood and warrants further investigation.
- Plant alkaloids, such as vincristine or vinblastine are associated with swelling of unmyelinated axons and of large diameter sensory neurons that can impair anterograde axonal transport, inducing a dose-dependent neuropathy.

Correlates of Neuropathy

- Pain (shooting, burning) can accompany chemotherapy-induced peripheral neuropathy. Some evidence indicates that fatigue and depression also may be common features in peripheral neuropathy.



9. Recommendations

This section is based on a review of the cited integrated reviews and clinical practice guidelines published on peripheral neuropathy (see Section 4 & 5).

Practice

Evidence suggests that toxicity-grading scales alone are inadequate in the early detection of chemotherapy-induced peripheral neuropathy. Consensus is lacking regarding what scale to use and there is inconsistent interpretation of toxicity scale information by clinicians and researchers.

- Employ clinical assessment using objective and subjective neuromuscular data to enhance the early detection of chemotherapy-induced peripheral neuropathy in addition to toxicity rating scales.
- Use a consistent method or scale to assess peripheral neuropathy, allowing for individual follow-up of neurologic changes over time.
- Assessment parameters should include subjective sensations of the presence of burning, pain, numbness, tingling. Objective assessment for motor and sensory signs such as gait, balance, muscle strength, proprioception, vibration, deep tendon reflexes and pinprick. Autonomic signs of neuropathy such as orthostatic blood pressure, pulse variation and Valsalva's maneuver should also be assessed routinely.
- Range of motion and resistance exercises may be helpful with reinnervation and in combating muscle weakness.
- Assess whether assistive devices are needed to improve gait and balance.

Education

- All patients should receive information regarding the specific neurotoxic effects expected from their chemotherapy regimen.
- All patients receiving neurotoxic chemotherapy should be taught motor, sensory, and autonomic neurologic signs and symptoms to report to their healthcare providers.
- Nurses caring for patients with cancer need ongoing training in the conduct and interpretation of clinical measures of neuropathy (i.e., deep tendon reflexes, muscle strength measurement, and grading).

Research

- Consensus still is lacking as to what specific factors are most important in determining the severity of peripheral neuropathy. Further research is needed to examine which signs and symptoms, and the degree of symptomatology, are most indicative of functional impairment resulting from neuropathy.
- Reach a consensus on a definition of neuropathy and use consistent measures that are reliable and valid to permit study result comparisons. A standard definition of the physiological changes that comprise a diagnosis of chemotherapy-induced peripheral neuropathy is lacking but necessary to advance the science in this area. Using the same consistent reliable and valid measures would eliminate some of the methodological issues inherent in the current CIPN research.
- Development of a comprehensive peripheral neuropathy scale that includes subjective, objective and quality-of-life impact specific to peripheral neuropathy is needed.
- Research is needed regarding the neuropathy experience in diverse and older populations.
- Studies of chemotherapeutic agents may need to be replicated using newer agents and/or dose-dense treatment schedules to appropriately determine the amount and severity of peripheral neuropathy.
- Studies of the effects of known neurotoxic cancer agents when administered to individuals with pre-existing neuropathies (e.g., diabetes, HIV-neuropathy) are needed.
- Studies examining the relationship between the development of peripheral neuropathy and cancer treatment adherence are needed.
- Further trials of neuroprotective agents, calcium and magnesium infusions and neurotrophic factors are needed before these agents can be recommended for routine use in practice.

10. Links

Cancer Symptoms: <http://www.cancersymptoms.org/>

(Peripheral Neuropathy available summer, 2005)

Guidelines Clearinghouse: <http://www.guidelines.org/>

Guideline for the Use of Neurontin in the Management of Neuropathic Pain

Advances in Neuropathic Pain: Diagnosis, Mechanisms and Treatment

Quantitative Sensory Testing: Report of the Therapeutics and Technology Assessment

Subcommittee of the American Academy of Neurology

American Society of Clinical Oncology: <http://www.asco.org/>

Clinical Practice Guidelines for the Use of Chemotherapy and Radioprotectants



11. Current Research

ONS Foundation-funded research (<http://www.ons.org/research/funding/projects/index.shtml>)

“Characterization of Biotherapy Induced Peripheral Neuropathy”, Constance Visovsky, PhD, RN, ACNP, Case Western Reserve University

National Institutes of Health-funded research (<http://crisp.cit.nih.gov/>)

International Cancer Research Portfolio (<http://www.cancerportfolio.org/>)

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