Chemotherapy-induced Peripheral Neuropathy Fact Sheet

What is chemotherapy-induced peripheral neuropathy?
Chemotherapy-induced peripheral neuropathy (CIPN) describes the damage to the peripheral nervous system incurred by a patient who has received a chemotherapeutic agent that is known to be neurotoxic. Neurotoxic side effects are the second most common acute side effect, behind hematologic toxicity[1]. A systematic review and meta-analysis, which included 4,179 patients using many classes of neurotoxic drugs, reports the incidence of CIPN to be 68.1% within the first 30 days after completing chemotherapy[2]. Table 1 describes symptoms caused by drugs in commonly used classes of neurotoxic chemotherapy agents. While each class of agents has its own mechanism of action, the CIPN that develops is thought to be a length dependent neuropathy that affects distal sites first, and as cumulative doses increase symptoms progress in severity and to more proximal areas. Sensory symptoms and signs typically develop before motor symptoms and a subset of patients will develop painful CIPN[3,4]. Patients with pre-existing peripheral neuropathy may develop a more severe and persistent CIPN[1,2,5]. The symptoms associated with CIPN will often improve or completely resolve, but there are a significant number, 30-83%, who will have a persistent neuropathy[2,6-8]. The estimate varies widely based on measures of neuropathy and chemotherapy regimens studied.

Table 1. Commonly used chemotherapy agents associated with peripheral neuropathy

	Incidence of Peripheral Neuropathy	Sensory Symptoms	Motor Symptoms	Other common side-effects
ANTIMICROTUBULE AGENTS Paclitaxel (Taxol®) Docetaxel (Taxotere®) Abraxane™ Vincristine (Onkovin®) Vinorelbine (Navelbine®) Ixabepilone (Ixempra®)	 60%[4] 50%[5] 71%[6] Not listed 25%[9] 63%[10]	Mild to moderate numbness, tingling, burning/stabbing pain of hands and feet are common and can become severe with increased doses[9,11]	Weakness of distal muscles, decreased deep tendon reflexes, and foot drop have been noted with high doses[5,9,11]	Granulocytopenia, neutropenia, leukocytopenia, anemia, myalgia,arthralgia, fatigue, nausea, alopecia[9,11]
PLATINUM COMPOUNDS: Cisplatin (Platinol®) Carboplatin (Paraplatin®) Oxaliplatin (Eloxatin®)	 Not listed 4%[12] 74%[13]	Mild to moderate numbness and tingling of hands and feet can occur after prolonged (4-6 months) therapy and may develop 3-8 weeks after last dose.[14] Symptoms can become severe with high cumulative doses[14] Reduced or absent Achilles tendon reflex[15]. Oxaliplatin can cause acute hypersensitivity to cold stimuli in the mouth, throat and hands[1]	Weakness is rare but can occur with high doses of Cisplatin and Oxaliplatin[13,14]	Ototoxicity[13,14], vestibular toxicity[14], anemia, neutropenia, leukocytopenia, thrombocytopenia, nausea[13,14]
TARGETED THERAPIES: Bortezomib (Velcade®)	31-55%[10]	Decreased sensation and numbness and tingling of the hands and feet. Those with preexisting neuropathy may experience a worsening of their neuropathy[16]	Myalgias and muscle cramps are less common side effects[16]	Fatigue, generalized weakness, nausea, vomiting, diarrhea, low platelet count, low red blood cell count, fever, constipation, poor appetite[16].
IMMUNOMODULATORY AGENTS: Thalidomide (Thalomid®)	25-83%[10]	Numbness and tingling and pain in the feet or hands[16]	Weakness[16]	Fatigue, confusion, mood changes, skin rashes, constipation[16]

How should I screen for CIPN?
There are other disease or treatment related impairments that may present similarly to CIPN. Pattern of presentation, timing of symptom onset and progression of symptoms are helpful when differentiating CIPN from other impairments. It is important to perform a thorough history and/or chart review to identify if the patient has had any of the above listed drugs as part of their treatment regimen. If so, then further screening for CIPN is warranted. The most common subjective complaint is numbness or tingling of the fingers or toes[1,17]. If weakness is a component, it will be symmetrical distal weakness. More proximal weakness may be indicative of steroid related myopathy and unilateral weakness indicative of central or other peripheral nerve impairment (i.e. brain/spinal cord metastases or nerve plexus compression by tumor).

Another common complaint is pain in the hands or feet. However, if the patient is complaining of pain only in the hands, but not the feet, drug related arthralgia or myalgia should be considered, because CIPN is a length dependent impairment that typically presents in the feet first. There are many excellent neuropathic pain screening tools, which will also help differentiate neuropathic pain from musculoskeletal pain. The Douleur Neuropatique-4 (DN4) and Self-Report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS), are validated tools with strong predictive value for identifying individuals with neuropathic pain[18-20].

How should I assess CIPN?
Several measures which quantify the severity of CIPN are described below. In addition, measures of pain, postural control (balance), and hand dexterity are useful to document impairments in body structure/function and limitations in activities/participation through the treatment and survivorship spectrum of care.

Tables 2 and 3 summarize the measures to quantify the severity of CIPN and balance impairments respectively. The tables include the Breast Cancer Evaluation Database to Guide Effectiveness (EDGE) taskforce ratings for each measure[21,22]. This fact sheet only includes measures that rated 2A or higher. There has not been an EDGE rating of fine motor scales for breast cancer patients.

Table 2. Measures of Chemotherapy-induced Peripheral Neuropathy Severity

Measure	Summary	Psychometrics*	EDGE rating
Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) (v4)[23]	• An 11-item patient self-report tool that describes CIPN symptom severity and functional consequences. • 0-44 points, a higher score indicates better quality of life	VALIDITY Content: developed with clinician and survivor input Internal Consistency: Cronbach's α = 0.62-0.90, 0.82-0.86, 0.80-0.85 Convergent: r=0.39-0.64 with objective PN measures Discriminant: ($p<0.001$) vs. cancer pts with no neurotoxic chemo exposure in ovarian and endo Ca Criterion: 0.81 AUC for ROC of NCI-CTC grade 1-4 vs. grade 0 in endo Ca • Score of 25 may distinguish dose-limiting ntx (sens = 1.0, spec = 0.85) RELIABILITY Cautiously assumed from validity[24]	4

Chemotherapy-induced Peripheral Neuropathy Assessment Tool (CIPNAT)[25]	• A 50-question patient self-report tool that quantifies their symptom experience (0-279) and activity interference (0-140). • A higher score in each area indicates worse symptoms and worse interference respectively.	VALIDITY Content: developed by expert panel using survivor interview data[25] Internal Consistency: Cronbach's α = 0.91-0.95[25] Convergent: r = 0.83 FACT/GOG-Ntx[25] Discriminant: ($p \leq 0.001$) pt on neurotoxic chemo vs. Ca pt on non-neurotoxic chemo RELIABILITY Test-retest:[25] 0.93 Total scale 0.89 Symptoms 0.93 Interference	2A
European Organization for Research & Treatment in Cancer Quality of Life Quest –CIPN 20 Item (EORTC QLQ-CIPN 20)[26]	• A 20-item patient self-report tool to assess symptoms and function in the sensory, motor and autonomic domains. • 0-80, a higher score indicates worse neuropathy.	VALIDITY Content: based on clinician & survivor input[27] Construct: 3-subscale model (sensory, motor, autonomic) could not be validated in confirmatory factor analysis; Exploratory analysis suggested 2-factor structure for 16-item reduction (lower & upper extremity)[28] Internal Consistency: Cronbach's α = 0.73-0.82[27], 0-78-0.88[28] Convergent:[28] r=0.36-0.57 with BPI-SF severity r=0.20 with NCI-CTC Discriminant: ($p \leq 0.0001$) vs. cancer pts with no neurotoxic chemo exposure[28] RELIABILITY Test-retest:[26] 0.84 Sensory 0.84 Motor 0.73 Autonomic	2A
Modified Total Neuropathy Score (mTNS)[17]	• A 6-item tool that combines patient report of subjective sensory and motor symptoms, deep tendon reflexes, manual muscle testing of distal muscles, pin sensibility, and quantitative vibration thresholds using a Biothesiometer®**. • 0-24 points, higher score indicates worse neuropathy.	VALIDITY Convergent:[17] r=0.99 with full TNS r=0.65 with TUG r=-0.64 with SOT r=-0.92 with FACT-taxane Discriminant: ($p \leq 0.001$) taxane exposed Ca survivors from matched healthy controls[17] RELIABILITY Intra-rater: ICC = 0.8955 (unpublished data Wampler et al, 2006)	2A

Total Neuropathy Score, clinical version (TNSc)[29]	• A 7-item tool that combines patient report of subjective sensory and motor symptoms, number of autonomic symptoms, deep tendon reflexes, manual muscle testing of distal muscles, pin sensibility, and semi-quantitative vibration sensibility using a graduated Rydel-Seiffer tuning fork. • 0-28 points, higher score indicates worse neuropathy.	VALIDITY Content: developed by expert panel & lit review[29] Convergent: r=0.36-0.80 with NCI-CTC & ECOG sensory and motor scores[29,30] RELIABILITY[29] Interrater: 0.85 Test-Retest: 0.86-0.87	2A
5-item reduced Total Neuropathy Score (TNSr 5-item)[31]	• A 5-item tool that combines patient report of subjective sensory symptoms, sharp sensibility using a pin, strength, tendon reflexes, vibration sensibility using a 128-hz tuning fork. • 0-20 points, higher score indicates worse neuropathy.	VALIDITY Content: All items except pain load on distinct factor when compared to Neuropathic Pain Scale[31] RELIABILITY Not available	2A

* More comprehensive list of psychometrics for each test can be found in the EDGE manuscript[21] and for other populations at www.rehabmeasures.org
** Age-based normative data for testing sites for the Biothesiometer[32]
Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; r, Pearson's coefficient correlation; PN, peripheral neuropathy; Ca, cancer; endo, endometrial; AUC, area under the curve; ROC, receiver operator curve; NCI-CTC, National Cancer Institute Common Terminology Criteria; BPI-SF, Brief Pain Inventory Short Form; TUG, timed up and go; SOT, sensory organization test; FACT-taxane, Functional Assessment Cancer Therapy-taxane; ICC, intraclass correlation coefficient, ECOG, Eastern Cooperative Oncology Group

Table 3. Measures of Balance

Measure	Summary	Psychometrics*	EDGE rating
Fullerton Advanced Balance Scale (FABS)[33]	• A battery of 10-tasks which challenge the visual, vestibular and somatosensory systems. • 0-40 points, higher score indicates better balance • <25/40 indicates higher fall risk for independently living older adults (cancer survivorship status was not documented in this study)[34] • risk of falling increases by 8% for each point scored below 25[34] • Administration instructions-- http://geriatrictoolkit.missouri.edu/fab/index.htm	VALIDITY Discriminant: (p =0.008) taxane exposed Ca survivors from matched healthy controls[17] Convergent: r= 0.581 with SOT[35] r=-0.496—0.581 with COP velocity on force plate[35] RELIABILITY Test-retest: ICC=0.92 in women with breast Ca[35]	3

Timed Up and Go (TUG)[36]	• Individual is instructed to stand up from a chair, walk 3 meters as quickly and safely as possible, turn around, walk back, and sit down. The test is timed. • A longer time indicates worse performance	VALIDITY Discriminative: (p = 0.020) taxane exposed Ca survivors from matched healthy controls[17] Convergent: r=-0.48 with SOT in breast Ca[35] Poor correlation with measures of physical functioning and number of falls[37] Did not significantly correlate to mTNS[38] RELIABILITY Test-retest: ICC=0.88, women with breast Ca[35]	3
Activities Specific Balance Confidence Scale (ABC)[39]	• A 16-item questionnaire that can be self-administered or given by interview. • Patients rate their confidence that they will not lose their balance or become unsteady for 16-tasks (0% represents no confidence to 100% represents complete confidence) • Overall score is calculated by adding items and then dividing by total number of questions answered • <67% represents increased fall risk[40]	VALIDITY Was not able to discriminate between fallers vs. non-fallers in adult cancer population[41] RELIABILITY Not established in cancer population	2A
Balance Evaluation Systems Test (BESTest)[42]	• A 36-item clinical balance assessment developed to assess 6 constructs of postural control • Total score of 108 points, calculated into a percentage score, a higher score indicates better balance • Training DVD available for purchase http://bestest.us/ • Shortened versions, mini-BEST and brief BEST are available	VALIDITY Discriminative: Cancer patients had significantly smaller functional reach compared to controls[43] Was not able to discriminate between fallers vs. non-fallers in adult cancer population[41] Convergent: Significant correlations with pain, fatigue, and mobility in adults with cancer[43] RELIABILITY Inter-rater reliability: Adults with cancer ICC= 0.98-0.99[43]	2A

Berg Balance Scale (BBS)[44]	• 14-item clinical test of balance using static and dynamic tasks • Total score of 56, higher score indicates better balance • Score <45 indicates higher fall risk in elderly residents of senior living environment[44]	VALIDITY <u>Convergent:</u> Did not significantly correlate to mTNS scores in adult cancer patients[38] RELIABILITY Not established in cancer population	2A
Repeated Sit to Stand	• There are various versions of the repeated sit to stand test, including 30-second sit to stand, 10 Times Sit to Stand, Five Time sit to stand tests • Primarily a measure of functional lower limb muscle strength, but may be useful in quantifying functional change of transitional movements	VALIDITY Variations of the sit to stand test have been used in cancer studies[45-48] RELIABILITY Not established in cancer population	2A
Functional Reach[49]	• A measure of the maximal distance an individual can reach forward while standing in a fixed position • There is a modified version for sitting and reaching[50]	VALIDITY Has been used to assess balance after yoga and tai chi interventions in breast cancer patients but no significant difference identified[51,52] RELIABILITY Not established in cancer population	2A
Short Physical Performance Battery (SPPB)[53]	• Clinical test of physical performance with 3-subscales (repeated chair stands, balance testing, and gait speed)	VALIDITY <u>Discriminative:</u> Able to detect impaired scores in 56% of individuals in prostate cancer study. Impairments were found in all 3-subscales.[54] <u>Convergent:</u> Moderate correlation with a measure of sarcopenia (r=0.62)[55] Was not associated with falls[55] RELIABILITY Not established in cancer population	2A

* Psychometrics for cancer patients included here. Psychometrics for other populations can be found at www.rehabmeasures.org

MEASURES TO QUANTIFY HAND DEXTERITY

GROOVED PEG BOARD TEST

- A timed test of a patient's ability to place pegs into a slotted board.
- Discriminative validity: impaired in patients with painful CIPN[56]
- High test-retest reliability[57]

How do I treat patients with CIPN?

The following are suggestions for treatment of CIPN. There have been few physical therapy intervention studies that have addressed this specific population; however, there are several case studies, animal studies, and studies of patients with diabetic and HIV peripheral neuropathy that may help guide the treatment of patients with CIPN.

Addressing Body Structure/Function Impairments:

Patients with CIPN need to be educated in strategies to increase their safety with daily activities, as they may have decreased touch thresholds which put them at risk for tissue injury. Interestingly, temperature detection thresholds do not appear to be impaired in patients with taxane-induced PN[56], but oxaliplatin does seem to affect temperature thresholds and cause hypersensitivity to cold of the mouth, throat and hands in the immediate days after infusion[1]. Teaching patients self-care tips to avoid and protect self from the cold in the immediate hours after infusion can be helpful. Some patients with CIPN will develop neuropathic pain which in severe cases is unrelenting and debilitating[58]. Monochromatic infrared photo energy (MIRE) therapy may decrease neuropathic pain, improve touch thresholds, and improve balance[59-63]. Low level laser has some early evidence in decreasing hypersensitivity to touch and cold in oxaliplatin neuropathy[64]. In addition, working with the medical team to manage neuropathic pain may improve function and quality of life[65]. There is also emerging evidence that aerobic exercise may improve nerve health[58,66-68]. Lastly, the use of night splints might be indicated in individuals reporting painful cramps at the calves and intrinsic muscles of the feet with unrelenting somatosensory complaints at night[69,70].

Addressing Activities/Participation Limitations:

Patients who present with CIPN may also present with functional mobility problems such as decreased hand dexterity, decreased postural control (balance), and impaired gait[56,71]. Unfortunately, there is limited research examining the efficacy of physical therapy treatment for patients with CIPN. Sensory retraining and task specific training may improve hand function. Strength, power, aerobic, sensor-based balance training, and orthotics have some evidence of efficacy in cancer patients[58,64,72,73]. Exercise interventions targeting strength and balance have also been shown to benefit patients with diabetic peripheral neuropathy, who have similar symptoms as patients with CIPN[74]. Exercises that challenge the visual, somatosensory, and vestibular systems may also be important components to balance retraining programs[75].

This Chemotherapy-induced Peripheral Neurupathy Fact Sheet for Health Professionais is a public service from APTA and the Oncology Section of the APT. It is not intended to be a comprehensive overview of this subject.

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