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Chemotherapy Induced Peripheral Neuropathy

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Alberta Health Services
CancerControl Alberta

Clinical Practice Guideline SUPP-010 – Version 1
www.ahs.ca/guru

Background

There were an estimated 220,400 new diagnoses of cancer in Canada in 2018, and it is estimated that one in two Canadians will develop cancer in their lifetime.[1] For patients undergoing cancer treatment, chemotherapy-induced peripheral neuropathy (CIPN) is a common treatment-related side effect that can have a significant negative impact on quality of life[2] and is associated with higher healthcare costs and resource use.[3] CIPN is defined as the injury or degeneration of peripheral nerve fibers caused by exposure to a neurotoxic chemotherapy agent. Patients experiencing CIPN may experience sensory symptoms such as paresthesia, dysesthesia (numbness, tingling, abnormal touch sensations), cold sensitivity, hyperalgesia or allodynia in the hands or feet in a stocking-glove distribution, as well as pain.[4,5] Motor symptoms may include loss of strength, muscle cramps, and spontaneous movements.[6]

The precise incidence and prevalence of CIPN varies according to the chemotherapeutic agent, dose, duration of exposure, and method of assessment, and there is likely significant underreporting.[5] Approximately two-thirds of patients experience CIPN in the first month following chemotherapy and half of these patients continue to experience CIPN after six months.[7,8] It is likely that the rate of CIPN will continue to rise as cancer treatments become more aggressive and patient survival rates improve.[9,10] The chemotherapy agents associated with the highest incidence are the platinum drugs (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine) and bortezomib.[5,11,12] In addition, newer classes of medications, including molecular targeted chemotherapeutics and immune checkpoint inhibitors, continue to be associated with CIPN.[10] Management of CIPN can lead to chemotherapy dose reductions, modifications and/or premature treatment discontinuation, adversely affecting treatment outcomes.

The purpose of this guideline is to provide clinical practice recommendations to members of multidisciplinary healthcare teams who screen, assess, and manage adult patients with chemotherapy-induced peripheral neuropathy in their daily clinical practice.

Guideline Questions

1. What are the recommended strategies for the assessment of CIPN?
2. What are the recommended strategies for the prevention of CIPN?
3. What are the recommended rehabilitation interventions for patients with CIPN?
4. What are the recommended pharmacologic treatments for CIPN?
5. What are the recommended strategies for ongoing management of patients with CIPN?

Search Strategy

The PubMed database was searched for relevant studies, guidelines and consensus documents published up to December 2018. The specific search strategy, search terms, and search results, are presented in Appendix A, and evidence tables are available upon request. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines from the following organizations were considered in the development of our recommendations: American Society of Clinical Oncology (ASCO), BC Cancer (BCC), and the National Comprehensive Cancer Network (NCCN).

Target Population

The following recommendations apply to adult cancer patients with chemotherapy-induced peripheral neuropathy.

Recommendations

1. Assessment

1.1 The diagnosis of CIPN is a diagnosis of exclusion; when a patient presents with neuropathic symptoms, clinicians should first investigate and rule out alternative possible causes, including cord compression, medications, infection, metabolic/endocrine disorders, environmental exposure, vascular or autoimmune disease, common nerve entrapments (e.g., carpal tunnel syndrome) and trauma.[10,13]

1.2 Prior to neurotoxic therapy, a baseline focused health assessment should be performed and recorded, identifying any pre-existing conditions that may predispose/exacerbate CIPN (see Table 1).[14,15] Since CIPN often progresses with dose accumulation, it is recommended that patients are actively assessed for signs and symptoms during chemotherapy, and intermittently thereafter.[5] The main goal of routine clinical assessment is to determine whether the patient is experiencing significant neuropathic symptoms that require intervention.

Table 1. Focused Health Assessment, adapted from BC Cancer (2018) and International Association for the Study of Pain Special Interest Group[14,15]

	Symptom Assessment	Physical Assessment

Normal	- Do you have any pre-existing damage to the nerves in your hands or feet?
	- Any contributing factors?
	  ○ Cancer diagnosis and treatments
	  ○ Temporal profile of chemotherapy treatment
	  ○ Medical history (e.g., diabetes, vitamin B deficiency, alcohol use)
	  ○ Medication profile
	  ○ Recent lab or diagnostic reports
		Vital Signs:
		- Frequency – as clinically indicated
		- Assess the patient for orthostatic hypotension and heart rate
		
		Bedside Sensory Testing:

Symptom Assessment		Physical Assessment
Onset	- When did the symptoms begin?	- Touch: cotton ball, paint brush - Vibration: tuning fork - Pinprick: pin, toothpick, cocktail stick - Cold: cold metal, tube with cold water, Lindblom roller - Warm: warm metal, tube with warm water, Lindblom roller **Observe Patient General Appearance:** - Observe gait as patient walks, and note any hesitation, stumbling, unsteadiness, holding onto walls - Observe for any involuntary movements, tremors, spasms, wrist or foot drop - Observe any difficulty with closing buttons, shaky handwriting, holding objects, keyboard use
Provoking/ Palliating	- What brings it on? - What makes it worse/better?	
Quality (last 24 hours)	- Can you describe symptoms? ○ *Sensory:* numbness, tingling, pain, burning ○ *Motor:* falls, tripping, muscle weakness, abnormal gait, paralysis ○ *Autonomic:* constipation, urinary dysfunction, sexual dysfunction, orthostatic hypotension - Are symptoms intermittent or constant?	
Region/ Radiation	- Where are you experiencing your symptoms? (e.g., toes, fingers, symmetrical)	
Severity/Other Symptoms	- How bothersome is this symptom to you on a scale of 0-10, where 0 is "not at all" and 10 is "the worst imaginable"? - Are there any accompanying symptoms? (e.g., pain)	
Treatment	- What medications or other strategies are you using right now? How effective are they? Are there any side effects? - What medications or strategies have been effective in the past?	
Understanding/ Impact	- Do your symptoms affect your role, function, mood, or ability to do activities of daily living? (e.g., buttoning a shirt, writing, picking up small items)	
Value	- What do you believe is causing this problem? - What is your comfort goal or acceptable level for this symptom, on a scale of 0-10?	

1.3 A valid quantitative measure should be used to assess the severity of motor symptoms, sensory symptoms, and pain. We recommend the use of the NCI-CTCAE v5 (Nervous System Disorders) and ESASr (Pain) tools regularly as needed at each appointment. Table 2 has been adapted from BC Cancer,[14] and summarizes these tools.

Table 2. CIPN Assessment Tools[14,16-18]

Peripheral Neuropathy Grading Scale				
Normal	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Peripheral Motor Neuropathy				
Normal	- Asymptomatic - Clinical or diagnostic observations only	- Moderate symptoms - Limiting instrumental ADLs (e.g., preparing meals, shopping, managing money)	- Severe symptoms - Limiting self-care ADLs (e.g., bathing, dressing, feeding self, using toilet, taking medications)	- Life-threatening consequences - Urgent intervention indicated
Peripheral Sensory Neuropathy				
Normal	Asymptomatic	- Moderate symptoms - Limiting instrumental ADLs (e.g., preparing meals, shopping, managing money)	- Severe symptoms - Limiting self-care ADLs (e.g., bathing, dressing, feeding self, using toilet, taking medications)	- Life-threatening consequences - Urgent intervention indicated

Pain Grading Scale				
0	**1 – 3**	**4 – 6**	**7 – 9**	**10**
No pain	Mild pain	- Moderate pain - Limiting instrumental ADLs (e.g., preparing meals, shopping, managing money)	- Severe pain - Limiting self-care ADLs (e.g., bathing, dressing, feeding self, using toilet, taking medications)	Worst possible pain

1.4 Patient reported outcome measures are important tools used to discuss the symptomology and severity of CIPN during clinic appointments. The FACT/GOG-Ntx is a patient reported outcome questionnaire with strong psychometric properties and acceptable reliability and validity; it is recommended for use in patients with gynecologic malignancies, however, additional studies are needed to determine validity in other cancer patient populations.[19-21] Similarly, the QLQ-CIPN20 is a patient reported outcome questionnaire intended to supplement the core quality of life questionnaire of the European Organization for Research and Treatment of Cancer (EORTC); while this tool has acceptable reliability and validity, it has been evaluated in only a limited number of studies.[20-22]

2. Prevention

Although several agents have been investigated for their efficacy in the prevention of CIPN, these studies have not demonstrated reliable or conclusive evidence of benefit to clinical practice. Limiting factors include small sample size, lack of placebo-controlled groups, un-blinded study designs, and the harms outweighing the benefits.[5,9,11,23,24] There are therefore currently no agents that can be recommended as a standard of care for the prevention of CIPN in patients with cancer undergoing treatment with neurotoxic agents.

2.1 Ensure patients are aware of the following before starting a chemotherapy regimen:

- Specific neurotoxic effects that can be expected from their chemotherapy regimen.
- Awareness of potential risk factors for CIPN, including prior chemotherapy, diabetes, folate/vitamin B12 deficiencies, history of smoking, and decreased creatinine clearance.[5,7]
- There are certain chemotherapy drugs such as paclitaxel and nab-paclitaxel that are associated with worsening of CIPN symptoms after completion of the last course of therapy.[25]
- Platinum neuropathy can progress for several months after completion of chemotherapy and can lead to permanent damage or limitations.[25,26]
- Signs and symptoms of platinum neuropathy (sensory, motor, autonomic) that should be reported to a health care provider when they are first noticed.
- Strategies for self-care and personal safety.

2.2 The following agents are ***not*** recommended for the prevention of CIPN:[23,24]

- Acetyl-L-carnitine (ALC)
- Amifostine

- Amitriptyline
- CaMg for patients receiving oxaliplatin-based chemotherapy
- Diethyldithio-carbamate (DDTC)
- Glutathione (GSH) for patients receiving paclitaxel/carboplatin-based chemotherapy
- Nimodipine
- Org 2766
- All-*trans*-retinoic acid

2.3 The efficacy of the following agents for the prevention of CIPN is ***inconclusive***:[23,24]

- *N*-acetylcysteine
- Carbamazepine
- Glutamate
- GSH for patients receiving cisplatin/oxaliplatin chemotherapy
- Goshajinkigan (GJG)
- Omega-3 fatty acids
- Oxcarbazepine
- rhuLIF
- Vitamin E
- Venlafaxine

2.4 Exercise

- There is a growing body of evidence to suggest a protective effect of exercise and physical activity on CIPN, particularly for patients treated with taxanes, platinum drugs, or vinca alkaloids.[27-30]
- More information is required regarding the optimal types of training (i.e., balance, strength, endurance) and recommended duration of exercise regimens; referral to a rehabilitation specialist is appropriate for patients who are experiencing changes in strength or mobility.

3. Rehabilitation

Cancer patients with CIPN often present with significant functional deficits, particularly as their neuropathy worsens. The most common deficits include decreased balance, gait abnormalities, muscle weakness, fine motor difficulties, and sensory loss, which can lead to an increased risk of falls, difficulties with performing activities of daily living (ADL), and safety concerns.[4] Rehabilitation specialists such as occupational therapists and physical therapists have a critical role in providing therapeutic interventions, education, and practical advice to help patients correct and manage their symptoms and improve their quality of life.[4,31-34]

3.1 CIPN rehabilitation referral criteria:

- Grade 2 CIPN according to NCI-CTCAE version 5 criteria (see Table 2; moderate pain and symptoms impacting instrumental ADLs such as preparing meals, shopping, managing money) and/or;
- Subsequent to an unsuccessful trial of initial pharmacologic therapy options (see Figure 1).

3.2 Assessments and outcome measures:

- ***General:*** quantitative sensory testing is a method of objectively quantifying and assessing sensory impairment. Is not sufficiently reliable to be used alone for decision making, but may be used as an adjunct to clinical assessment (monofilament protective sensation testing, reflex testing, vibration sensation testing, temperature testing, manual muscle testing of affected area).[4]
- ***Upper extremity specific:*** grip strength, DASH, functional task assessment, fine motor outcome measure (e.g., Jebsen Hand Function Test).
- ***Lower extremity specific:*** balance testing/assessment (Berg, TUG, FAB, mini-BEST), Gait assessment (Winters-Stone 2017).[35]
- ***Canadian Occupational Performance Measure:***[36]
  - Individualized measure of a patient's perception of problems encountered in occupational performance. Aims to provide high quality, occupation-focused, evidence-based, patient-centered practice.
- General assessment of ADL.

3.3 Recommended occupational therapy and physical therapy interventions are specific to each patient and their symptoms, and may include:[4,31,37-41]

- ***General:*** desensitization exercises, vibration desensitization, functional training/exercise, non-pharmacologic pain relief (TENS, ultrasound, acupuncture), assistive devices, education on safety/ adaptations, and sensory modification such as warm socks and gloves
- ***Upper extremity:*** therapeutic exercises, fine motor retraining, upper extremity, strengthening, adaptive equipment
- ***Lower extremity:*** footwear recommendations, gait aids, falls prevention education, balance exercises, gait re-training, foot orthotics, lower extremity strengthening, trial of compression, adaptive equipment

3.4 Recommended complementary therapies include relaxation techniques such as deep breathing, meditation, yoga, guided imagery, and massage.[14]

4. Pharmacological Management

Figure 1 outlines the recommended pharmacologic treatment approach for patients with painful established CIPN. The goals of pharmacologic therapy are:

- a reduction of pain by 30% or greater
- improved function (e.g., increased tolerance for walking and standing), mood, and sleep
- minimal or tolerable adverse effects

Good Practice Point: Guiding Principles for Administering Pharmacologic Therapy

- Titrate each agent up to usual minimum effective dose; if well tolerated and helpful, continue to titrate to the optimal dose.
- If an agent is ineffective and/or poorly tolerated, discontinue and consider an alternate agent.
- If an agent is only partially effective but well tolerated, continue it and add an additional agent or agents from a different class.
- Intractable pain may require treatment with some combination of agents such as anticonvulsants, antidepressants, and opioid analgesics. Opioids should be used with caution in patients with cancer that has been cured or is under long-term control.
- Individual patients and responses will vary, and every pain syndrome is unique, therefore the lack of evidence does not preclude reasonable attempts at symptom management.

4.1 For patients with CIPN symptoms that require pharmacological intervention, duloxetine is the only agent that has been shown in a well-designed randomized clinical trial to be effective in alleviating CIPN,[42] and is therefore the only recommended first-line medication. A subgroup analysis within the same trial suggested that duloxetine may be most effective for patients receiving platinum agents such as oxaliplatin compared to taxanes such as paclitaxel.[42] The recommended dosing is 30 mg per day for the first week, and 60 mg per day thereafter, if well tolerated.

4.2 The efficacy of the following agents is inconclusive for treatment of CIPN, but because their efficacy has been established for other forms of neuropathic pain and based on limited treatment options, it is reasonable to consider these agents either in addition to duloxetine, or if duloxetine is not effective or well-tolerated. Patients should be informed of the limited scientific evidence and counseled on the potential harms and benefits.[24]

- Anticonvulsants (gabapentin or pregabalin)
- Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, or imipramine)
- Referral to a specialized pain management service is recommended for discussion of other add-on or alternative options not described above.

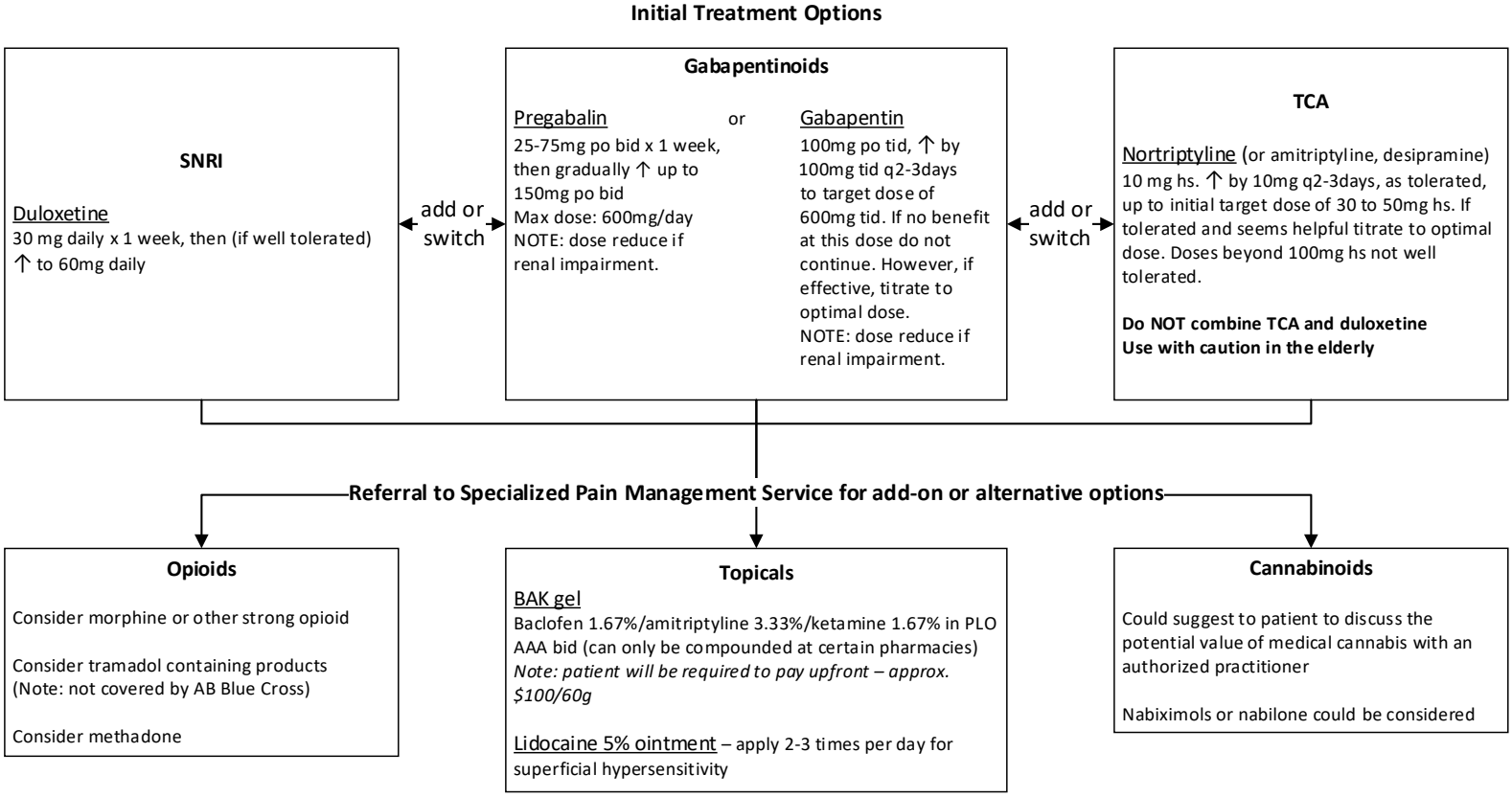
4.3 There is a lack of evidence regarding other pharmacologic treatments for the management of pain associated with CIPN. It may be reasonable to consider approaches that have shown efficacy in

general neuropathic cancer pain, including opioids, analgesics, and cannabinoids, for add-on or alternative options, as needed. Referral to a specialized pain management service is recommended for discussion of add-on or alternative options. For more information, please refer to the Cancer Pain clinical practice guideline.

4.4 For patients with CIPN with changing or worsening symptoms:[14]

- Rule out other causes or concomitant causes of symptoms or signs suggestive of peripheral neuropathy such as spinal cord compression.
- Active chemotherapy treatment may require treatment delays or reductions until symptoms resolve.

Figure 1. Suggested Approach for Medication Management of Pain Associated with CIPN[13,24,42]



AAA – apply to affected area, bid – twice daily, hs – at bedtime, po – by mouth or orally, TCA – tricyclic antidepressant, tid – three times a day

5. Referrals and Follow-up[14,31,32]

5.1 Refer cancer patients and survivors experiencing CIPN as clinically indicated:

- Physiotherapist
- Occupational Therapist
- Massage Therapist

- Acupuncturist
- Patient and Family Counseling
- Pain and Symptom Management/Palliative Care
- Home Health Nursing
- Neurologist – referral for nerve conduction studies, electromyography

References

1. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2019. Toronto, ON: Canadian Cancer Society; 2019. Available at: cancer.ca/Canadian-Cancer-Statistics-2019-EN
2. Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. Support Care Cancer 2014 Aug;22(8):2261-2269.
3. Pike CT, Birnbaum HG, Muehlenbein CE, Pohl GM, Natale RB. Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and nonsmall cell lung cancer. Chemother Res Pract 2012;2012:913848.
4. Stubblefield MD, Burstein HJ, Burton AW, Custodio CM, Deng GE, Ho M, et al. NCCN task force report: management of neuropathy in cancer. J Natl Compr Canc Netw 2009 Sep;7 Suppl 5:S-28.
5. Brewer JR, Morrison G, Dolan ME, Fleming GF. Chemotherapy-induced peripheral neuropathy: Current status and progress. Gynecol Oncol 2016 Jan;140(1):176-183.
6. Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. J Peripher Nerv Syst 2008 Mar;13(1):27-46.
7. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain 2014 Dec;155(12):2461-2470.
8. Pachman DR, Barton DL, Watson JC, Loprinzi CL. Chemotherapy-induced peripheral neuropathy: prevention and treatment. Clin Pharmacol Ther 2011 Sep;90(3):377-387.
9. Gutiérrez-Gutiérrez G, Sereno M, Miralles A, Casado-Sáenz E, Gutiérrez-Rivas E. Chemotherapy-induced peripheral neuropathy: clinical features, diagnosis, prevention and treatment strategies. Clin Transl Oncol 2010 Feb;12(2):81-91.
10. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. Ann Neurol 2017 Jun;81(6):772-781.
11. Argyriou AA, Kyritsis AP, Makatsoris T, Kalofonos HP. Chemotherapy-induced peripheral neuropathy in adults: a comprehensive update of the literature. Cancer Manag Res 2014;6:135-147.
12. Park SB, Goldstein D, Krishnan AV, Lin CS-, Friedlander ML, Cassidy J, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. CA Cancer J Clin 2013 Nov-Dec;63(6):419-437.
13. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Adult Cancer Pain, Version 2.2019, Accessed July 2019.
14. BC Cancer. Symptom Management Guidelines: Chemotherapy Induced Peripheral Neuropathy (CIPN), 2018. Accessed July 2019.
15. Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DLH, Bouhassira D, et al. Neuropathic pain: an updated grading system for research and clinical practice. Pain 2016 08;157(8):1599-1606.
16. National Cancer Institute - Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017. Accessed July 2019.
17. Watanabe SM, Nekolaichuk C, Beaumont C, Johnson L, Myers J, Strasser F. A multicenter study comparing two numerical versions of the Edmonton Symptom Assessment System in palliative care patients. J Pain Symptom Manage 2011 Feb;41(2):456-468.
18. Cancer Care Ontario. Algorithm: Pain in Adults with Cancer - Screening and Assessment, 2010. Accessed July 2019.
19. Calhoun EA, Welshman EE, Chang CH, Lurain JR, Fishman DA, Hunt TL, et al. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. Int J Gynecol Cancer 2003;13(6):741-748.
20. Cavaletti G, Frigeni B, Lanzani F, Mattavelli L, Susani E, Alberti P, et al. Chemotherapy-Induced Peripheral Neurotoxicity assessment: a critical revision of the currently available tools. Eur J Cancer 2010 Feb;46(3):479-494.
21. Curcio KR. Instruments for Assessing Chemotherapy-Induced Peripheral Neuropathy: A Review of the Literature. Clin J Oncol Nurs 2016 Apr;20(2):144-151.

22. Postma TJ, Aaronson NK, Heimans JJ, Muller MJ, Hildebrand JG, Delattre JY, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. Eur J Cancer 2005 May;41(8):1135-1139.
23. Albers JW, Chaudhry V, Cavaletti G, Donehower RC. Interventions for preventing neuropathy caused by cisplatin and related compounds. Cochrane Database Syst Rev 2014 Mar 31,(3):CD005228.
24. Hershman DL, Lacchetti C, Loprinzi CL. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline Summary. J Oncol Pract 2014 Nov;10(6):e42-e424.
25. Staff NP, Cavaletti G, Islam B, Lustberg M, Psimaras D, Tamburin S. Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment. J Peripher Nerv Syst 2019 Oct;24 Suppl 2:S26-S39.
26. Pachman DR, Weisbrod BL, Seisler DK, Barton DL, Fee-Schroeder KC, Smith TJ, et al. Pilot evaluation of Scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy. Support Care Cancer 2015 Apr;23(4):943-951.
27. Streckmann F, Zopf EM, Lehmann HC, May K, Rizza J, Zimmer P, et al. Exercise intervention studies in patients with peripheral neuropathy: a systematic review. Sports Med 2014 Sep;44(9):1289-1304.
28. Kleckner IR, Kamen C, Gewandter JS, Mohile NA, Heckler CE, Culakova E, et al. Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. Support Care Cancer 2018 Apr;26(4):1019-1028.
29. Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Friedenreich CM, Yasui Y, et al. Subgroup effects in a randomised trial of different types and doses of exercise during breast cancer chemotherapy. Br J Cancer 2014 Oct 28,;111(9):1718-1725.
30. Mols F, Beijers AJM, Vreugdenhil G, Verhulst A, Schep G, Husson O. Chemotherapy-induced peripheral neuropathy, physical activity and health-related quality of life among colorectal cancer survivors from the PROFILES registry. J Cancer Surviv 2015 Sep;9(3):512-522.
31. McNeely ML, Dolgoy N, Onazi M, Suderman K. The Interdisciplinary Rehabilitation Care Team and the Role of Physical Therapy in Survivor Exercise. Clin J Oncol Nurs 2016 12 01,;20(6 Suppl):S8-S16.
32. Kim JH, Dougherty PM, Abdi S. Basic science and clinical management of painful and non-painful chemotherapy-related neuropathy. Gynecol Oncol 2015 Mar;136(3):453-459.
33. Harris SR, Schmitz KH, Campbell KL, McNeely ML. Clinical practice guidelines for breast cancer rehabilitation: syntheses of guideline recommendations and qualitative appraisals. Cancer 2012 Apr 15,;118(8 Suppl):2312-2324.
34. Visovsky C, Collins M, Abbott L, Aschenbrenner J, Hart C. Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. Clin J Oncol Nurs 2007 Dec;11(6):901-913.
35. Winters-Stone KM, Horak F, Jacobs PG, Trubowitz P, Dieckmann NF, Stoyles S, et al. Falls, Functioning, and Disability Among Women With Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy. J Clin Oncol 2017 Aug 10,;35(23):2604-2612.
36. Law M, Baptiste S, McColl M, Opzoomer A, Polatajko H, Pollock N. The Canadian occupational performance measure: an outcome measure for occupational therapy. Can J Occup Ther 1990 Apr;57(2):82-87.
37. Wong R, Major P, Sagar S. Phase 2 Study of Acupuncture-Like Transcutaneous Nerve Stimulation for Chemotherapy-Induced Peripheral Neuropathy. Integr Cancer Ther 2016 06;15(2):153-164.
38. Cammisuli S, Cavazzi E, Baldissarro E, Leandri M. Rehabilitation of balance disturbances due to chemotherapy-induced peripheral neuropathy: a pilot study. Eur J Phys Rehabil Med 2016 Aug;52(4):479-488.
39. Verhulst ALJ, Savelberg, Hans H. C. M., Vreugdenhil G, Mischi M, Schep G. Whole-Body Vibration as a Modality for the Rehabilitation of Peripheral Neuropathies: Implications for Cancer Survivors Suffering from Chemotherapy-Induced Peripheral Neuropathy. Oncol Rev 2015 Feb 10,;9(1):263.
40. Stubblefield MD, McNeely ML, Alfano CM, Mayer DK. A prospective surveillance model for physical rehabilitation of women with breast cancer: chemotherapy-induced peripheral neuropathy. Cancer 2012 Apr 15,;118(8 Suppl):2250-2260.
41. Wong R, Sagar S. Acupuncture treatment for chemotherapy-induced peripheral neuropathy--a case series. Acupunct Med 2006 Jun;24(2):87-91.
42. Smith EML, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA 2013 Apr 03,;309(13):1359-1367.

Appendix A: Literature Search Strategies and Results

Table 1. PubMed Literature Search Strategy for Assessment of CIPN

#1	"peripheral nervous system diseases"[MeSH Terms] AND "drug therapy"[MeSH Terms] AND "neoplasms"[MeSH Terms]	1363
#2	"symptom assessment"[MeSH Terms] OR "symptom assessment"[All Fields]	17139
#3	diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "diagnosis"[MeSH Terms]	2408533
#4	"risk factors"[MeSH Terms] OR "risk factors"[All Fields]	495696
#5	#2 OR #3 OR #4	2643608
#6	#1 AND #5	328
#7	Limit #6 to Publication Date from 2012/01/01 to 2019/01/01; Humans; English; Article Types: Practice guideline or Review or Systematic review	36

Table 2. PubMed Literature Search Strategy for Prevention of CIPN

#1	"peripheral nervous system diseases"[MeSH Terms] AND "drug therapy"[MeSH Terms] AND "neoplasms"[MeSH Terms]	1363
#2	"prevention and control"[Subheading] OR "prevention"[All Fields]	1629421
#3	"neuroprotection"[MeSH Terms] OR "neuroprotection"[All Fields]	23144
#4	#2 OR #3	1648251
#5	#1 AND #4	119
#6	Limit #5 to Publication Date from 2012/01/01 to 2019/01/01; Humans; English	50

Table 3. PubMed Literature Search Strategy for Pharmacological Treatment of CIPN

#1	"peripheral nervous system diseases"[MeSH Terms] AND "drug therapy"[MeSH Terms] AND "neoplasms"[MeSH Terms]	1363
#2	("pharmacology"[MeSH Terms] OR "pharmacology"[All Fields] OR "pharmacologic"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])	1355435
#3	#1 AND #2	109
#4	Limit #3 to Publication Date from 2007/01/01 to 2019/01/01; Humans; English	56

Additional Criteria: Review articles, case reports with <30 patients, and studies that did not report on the outcomes of interest were excluded from the final review were not included in the final review.

Table 4. PubMed Search Strategy for **Rehabilitation Recommendations for CIPN**

#1	"peripheral nervous system diseases"[MeSH Terms] AND "drug therapy"[MeSH Terms] AND "neoplasms"[MeSH Terms]	1363
#2	("rehabilitation"[Subheading] OR "rehabilitation"[All Fields] OR "rehabilitation"[MeSH Terms]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])	30411
#3	"physical therapy modalities"[MeSH Terms]	142531
#4	"exercise therapy"[MeSH Terms] OR "exercise therapy"[All Fields]	110642
#5	“acupuncture"[MeSH Terms] OR "acupuncture therapy"[MeSH Terms]	29921
#6	#2 OR #3 OR #4 OR #5	249448
#7	#1 AND #6	48
#8	Limit #7 to Publication date from 2012/01/01 to 2019/01/01; Humans; English	22

Additional Criteria: Review articles, case reports with <5 patients, and studies that did not report on the outcomes of interest were excluded from the final review. A hand-search of the initial resulting references led to 4 additional articles being included in the final evidence table.

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Palliative Care Tumour Team. Evidence was selected and reviewed by a working group comprised of a medical oncologist, a palliative care physician, two nurse practitioners, a pharmacist, an occupational therapist, and a knowledge management specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in November, 2019.

Maintenance

A formal review of the guideline will be conducted in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

ADL, activities of daily living; ALC, acetyl-L-carnitine; CIPN, chemotherapy-induced peripheral neuropathy; DDTC, diethyldithio-carbamate; ESASr, Edmonton Symptom Assessment System-revised; GJG, goshajinkigan; GSH, glutathione; NCI-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events; rhuLIF, recombinant human leukemia inhibitory factor; TENS, transcutaneous electrical nerve stimulation

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Palliative Care Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

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