NCCN Task Force Report: Management of Neuropathy in Cancer

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Abstract
Neuropathy is a common, often debilitating complication of cancer and its treatment. Effective management of this disorder depends on early diagnosis and an understanding of its underlying causes in the individual patient. In January 2009, NCCN gathered a multidisciplinary group to review the literature and discuss intervention strategies currently available to patients as well as areas that require research efforts. The task force, which comprised experts in anesthesiology, medical oncology, neurology, neuro-oncology, neurophysiology, nursing, pain management, and rehabilitation, was charged with the goal of outlining recommendations for the possible prevention, diagnosis, and management of neuropathy. This report documents the proceedings of this meeting with a general background on neuropathy and neuropathy in oncology, followed by discussions on challenges and research issues, evaluation criteria, and management of different symptoms associated with this disorder. (JNCCN 2009;7[Suppl 5]:S1-S26)

Overview
What Is Neuropathy?
Neuropathy, or peripheral neuropathy, is defined as the condition arising from the damage and dysfunction of the peripheral nerves—the motor, sensory and autonomic nerves that connect the brain and spinal cord to the rest of the body. The major anatomic demarcations of the peripheral nervous system include the nerve root, plexus, and peripheral nerves. Although the terms neuropathy and peripheral neuropathy generally refer to the part of the nervous system distal to the plexus, it should be noted that any or all levels of the peripheral nervous system may be affected depending on the etiology of insult. There are more than 100 known types of neuropathy, each with its specific prognosis, set of symptoms, and progressive pattern.

Neuropathy is most common in people over age 55, with a prevalence of 3% to 4%. Among the general population, about a third of cases are caused by diabetes, while another third is termed idiopathic (cause unknown). Neuropathy can also result from a variety of factors, including medications (such as chemotherapeutic agents), genetics, autoimmune disorders, infections, nutritional deficiencies, and metabolic imbalances. Neuropathy is a common complication of cancer and its treatment that can lead to serious clinical consequences for the patient. This report presents the views of the NCCN Task Force on the assessment and management of neuropathy in cancer patients as discussed at the meeting in January 2009.

Signs and Symptoms
The severity of neuropathy ranges from discomfort to being severely debilitating, and the onset of symptoms can be sudden or slowly progress over time. Initially, patients often feel abnormal sensations like tingling, pain, or numbness. Many complain of difficulty in walking, dropping things, or feeling like they are wearing gloves and stockings when they are not. If internal organs are affected, patients may experience diarrhea or constipation, low blood pressure, irregular heartbeat, or even difficulty breathing.

Neuropathy in Cancer
Consequences of neuropathy can be severe for patients with cancer and may result in reduced quality of life, interference with activities of daily living, disability, and potentially shorter survival. Neuropathic symptoms resulting from therapeutic interventions such as the chemotherapy can cause treatment delays, dose reductions, or even discontinuation of therapy, which can affect outcomes and compromise survival.
Patients with cancer have a heightened risk of developing neuropathy. Cancer-related causes include:

- Neurotoxicity of cancer treatment, such as surgery, radiotherapy, and chemotherapy (addressed further in detail)
- Tumor pathology: direct compression or infiltration of nerves by primary or metastatic lesions
- Nutritional deficiencies
- Metabolic disturbances
- Opportunistic infections
- Paraneoplastic neurologic disorders (PND), or nervous dysfunction caused by the remote effects of cancer

**Chemotherapy-Induced Peripheral Neuropathy**

Neuropathy is a major dose-limiting toxicity of many chemotherapeutic regimens. Among the various types of neuropathies seen in cancer patients, chemotherapy-induced peripheral neuropathy (CIPN) is the most widely reported and has been the focus of research efforts. For these reasons, much of the panel discussion and conclusions is focused on CIPN.

CIPN usually manifests as sensory symptoms such as paresthesia and dysesthesia (numbness, tingling, abnormal touch sensations), or cold sensitivity. Pain is often reported and may be described as burning, freezing, lancination, shock-like, or electric. Normal touch can be perceived as painful (allodynia), with sensations that would normally be painful experienced as excruciating (hyperpathia). Motor symptoms are uncommon and usually milder. These may manifest as mild weakness in the lower limbs. Reflexes at the ankles may be diminished or absent. Some patients experience altered proprioception, which can lead to accidents or falls. Autonomic impairment is thought to be rare, although this has not been systematically studied. Evidence of this impairment might include constipation after use of vinca alkaloids, orthostasis, urinary dysfunction, and sexual dysfunction.

CIPN has a number of diagnostic features that can help physicians distinguish it from other neuropathies (e.g., PND, carpal tunnel syndrome, diabetic neuropathy, metabolic neuropathy). These are:

- Symmetrical, distal, length-dependent “glove and stocking” distribution
- Predominantly sensory symptoms (especially pain), both in frequency and severity, rather than motor symptoms
- Onset after administration of chemotherapy, which may be progressive, rapid, or “coasting”
- Dose-dependent

Table 1 is a general but not exhaustive list of chemotherapeutic drugs and anticancer biologics frequently reported as associated with symptomatic neuropathy. These include platinum-containing agents, vinca alkaloids, taxanes, bortezomib, thalidomide, lenalidomide, and ixabepilone. Many of these drugs (e.g., paclitaxel and cisplatin) are widely used in a variety of cancers. The onset dose is an approximation of the cumulative dose when neuropathy typically starts to occur. For most regimens, severity of neuropathy increases with dose and duration until cessation of treatment. A notable exception is the platinum agents, for which symptoms may progress for weeks to months after treatment completion. This is called the *coasting effect*.

Another exception to the typical pattern of CIPN is oxaliplatin, which is unique in that 2 patterns have been observed: acute transient (cold-induced) and cumulative persistent (dose-limiting) neuropathy. Symptoms of CIPN usually subside with time for most drugs, although long-term sequelae can occur.

**Challenges in Oncology and Research Issues**

Despite the high overall reported occurrence across different cancers, data on neuropathic toxicity appears scattered and at times confusing, especially for older drugs such as cisplatin or vincristine. Historically, CIPN has not been a research focus in chemotherapeutic medicine. Neurotoxicity is typically reported as one of many adverse events in clinical trials the goal of which is to test other health outcomes (e.g., response or survival), and this broadly defined term renders comparison across studies difficult.

As shown in Table 1, the frequency of documented neuropathic events ranges widely for many agents. One main reason is that the severity and frequency of the adverse effects heavily depends on the dose, duration, and schedule. This can be illustrated using paclitaxel given to breast cancer patients: a dose of 175 mg/m² is associated with 2% to 12%, grade 3 to 4 sensory neuropathy (based on the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]), compared with 22% to 33% for a dose of 250 mg/m² (infusion over 3 hours every 3 weeks for either dose). Within the same trial, increasing the infusion period from 3 to 24 hours at the 250 mg/m² dose re-
### Table 1  Common Antineoplastic Agents Known to Induce Neuropathy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence</th>
<th>Onset Dose</th>
<th>Clinical Manifestation</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platinum compounds</strong></td>
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<tr>
<td>Cisplatin</td>
<td>28%–100% (overall)</td>
<td>300 mg/m²</td>
<td>Symmetrical painful paresthesia or numbness in a stocking-glove distribution, sensory ataxia with gait dysfunction</td>
<td>Partial, symptoms may progress for months after discontinuation</td>
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<tr>
<td>+ paclitaxel: 7%–8% (severe*)</td>
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<tr>
<td>Carboplatin</td>
<td>6%–42% (overall)</td>
<td>800–1600 mg/m²</td>
<td>Similar to cisplatin but milder</td>
<td>Similar to cisplatin</td>
</tr>
<tr>
<td>+ paclitaxel: 4%–9% (severe)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin (acute)</td>
<td>85%–95% (overall)</td>
<td>any</td>
<td>Cold-induced painful dysesthesia</td>
<td>Resolution within a week</td>
</tr>
<tr>
<td>Oxaliplatin (persistent/</td>
<td></td>
<td>750–850 mg/m²</td>
<td>Similar to cisplatin</td>
<td>Resolution in 3 months, may persist long-term</td>
</tr>
<tr>
<td>chronic)</td>
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<tr>
<td><strong>Vinca alkaloids</strong></td>
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<tr>
<td>Vincristine, vinblastine,</td>
<td>30%–47% (overall)</td>
<td>4–10 mg</td>
<td>Symmetrical tingling paresthesia, loss of ankle stretch reflexes, constipation, occasionally weakness, and gait dysfunction</td>
<td>Resolution usually within 3 months, may persist for vinristine</td>
</tr>
<tr>
<td>vinorelbine, vindesine</td>
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<tr>
<td><strong>Taxanes</strong></td>
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<tr>
<td>Paclitaxel</td>
<td>57%–83% (overall),</td>
<td>100–300 mg/m²</td>
<td>Symmetrical painful paresthesia or numbness in stocking-glove distribution, decreased vibration or proprioception, occasionally weakness, sensory ataxia, and gait dysfunction</td>
<td>Resolution usually within 3 months, may persist</td>
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<tr>
<td>2%–33% (severe)</td>
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<tr>
<td>+ Cisplatin: 7%–8% (severe)</td>
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<tr>
<td>+ Carboplatin: 4%–16% (severe)</td>
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<tr>
<td>Abraxane (albumin-bound</td>
<td>73% (overall)</td>
<td>unclear</td>
<td>Similar to paclitaxel</td>
<td>Resolution usually within 3 weeks</td>
</tr>
<tr>
<td>paclitaxel)</td>
<td>10%–15% (severe)</td>
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<tr>
<td>Docetaxel</td>
<td>11%–64% (overall)</td>
<td>75–100 mg/m²</td>
<td>Similar to paclitaxel</td>
<td>Resolution usually within 3 months, may persist</td>
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<tr>
<td>3%–14% (severe)</td>
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<tr>
<td><strong>Others</strong></td>
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<tr>
<td>Bortezomib</td>
<td>31%–55% (overall)</td>
<td>1.3 mg/m²</td>
<td>Painful paresthesia, burning sensation, occasionally weakness, sensory ataxia, and gait dysfunction. Rare autonomic dysfunction including orthostatic hypotension</td>
<td>Resolution usually within 3 months, may persist</td>
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<tr>
<td>9%–22% (severe)</td>
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<tr>
<td>Ixabepilone</td>
<td>63% (overall), 14% (severe) + capecitabine:</td>
<td>40–120 mg/m²</td>
<td>Painful paresthesia, burning sensation</td>
<td>Resolution in 4–6 weeks</td>
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<tr>
<td>67% (overall), 21% (severe)</td>
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<tr>
<td>Thalidomide</td>
<td>25%–83% (overall), 15%–28% (severe)</td>
<td>20 g</td>
<td>Symmetrical tingling or numbness, pain. Occasionally tingling numbness, sensory ataxia, and gait dysfunction</td>
<td>May persist for over 1 year</td>
</tr>
<tr>
<td>Lenalidomide (thalidomide</td>
<td>10%–23% (overall), 1%–3% (severe)</td>
<td>unclear</td>
<td>Similar to thalidomide</td>
<td>Unclear</td>
</tr>
<tr>
<td>analog)</td>
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</table>

* Dose-limiting or grade 3 or 4 neuropathy according to the grading scale used by the study authors.
duced the incidence of severe neuropathy from 22% to 13%, while the increasingly adopted weekly schedule of 1-hour infusion (80 mg/m^2) increased neuropathic events compared with the conventional 3-hour infusion (175 mg/m^2) every 3 weeks (24% vs. 12%). Also, chemotherapy regimens often include more than one potentially neurotoxic drug, and the potential additive or synergistic effects of different drug combinations remain largely elusive.

In addition, cancer patients may have pre-existing peripheral nervous system dysfunction such as radiculopathy from degenerative disease or neuropathy from diabetes or other causes. This can predispose them to manifesting earlier and more severe neuropathic symptoms when challenged with a neurotoxic chemotherapeutic or other cancer-related insult. By the nature of the modern medical system, most cancer patients enrolling in a clinical trial have advanced disease and have already been exposed to a number of chemotherapeutic drugs, many of which may be neurotoxins. This poses significant difficulty in properly attributing subsequent neuropathy to the agent or regimen tested. For example, in a trial of 113 advanced breast cancer patients who have been heavily pretreated, mild peripheral neuropathy (grade 1–2) was already evident in 27% of the women before administration of the neurotoxic ixabepilone. Similarly, Richardson et al. documented an 81% and 83% baseline incidence of symptomatic neuropathy before bortezomib treatment based on patient questionnaires and neurologist examination reports, respectively, in a group of 256 patients with recurrent/relapsed myeloma. In the group, 11% also had a history of diabetes, which may have contributed to the development of CIPN.

Unfortunately, these 2 studies are among the few that include such complete information. The Task Force panelists expressed concern about the lack of standardization in quality reporting of CIPN. Across clinical trials, neuropathic cases have been recorded in a number of formats: specific symptoms (e.g., pain), development of functional impairment resulting from symptoms, neurophysiologic testing, and prevalence by grade or incidence of only severe cases according to different scoring systems. Even when the same scale is used, grading can vary due to differences in training and experience in patient assessment.

Compounding the problem is the issue of underreporting. Most clinical trials rely on patient self-report of symptoms rather than active query by the evaluator. Such voluntary symptom reporting can be influenced by patient personality, physician-patient relationship, and the medical system in which the study is conducted. The subjective nature of CIPN symptoms adds to the variability of reported incidence and severity. Underestimation and underreporting of CIPN are also suggested by studies that show that physician evaluation results in lower pain assessments than invited patient questionnaire. Admittedly, most existing evaluation tools are designed to measure neuropathy in other settings (e.g., diabetes) and have not been validated for CIPN. More sensitive and comprehensive assessment systems are needed for the chemotherapy setting.

Terminology clarification is also important for differential diagnosis. Panelists noted that health professionals and patients are often confused about the various medical terms describing pain (pain, neuropathy, paresthesia, dysesthesia), and with the different clinical conditions associated with pain. A patient experiencing paclitaxel-induced arthralgia is a classic example. Arthralgia is a transient, inflammatory joint pain that typically develops 24 to 48 hours after infusion and persisting for 3 to 5 days, as opposed to the symmetrical glove-stocking distribution of numbness, tingling, or burning related to CIPN that progresses with accumulating dose. However, the patient may only complain of a generic “pain” during a doctor visit. Becoming familiar with the clinical diagnostic features of CIPN and asking specific questions will help the evaluator identify the condition and implement proper intervention, such as dose reduction.

Quality assessment and reporting leading to accurate diagnosis is a crucial step that must precede clinical decisions regarding treatment. Unfortunately, CIPN presents a diagnostic dilemma because, to date, approved, effective treatment options are lacking. Although many therapeutic agents to treat or prevent CIPN have been proposed over the years, few are supported by adequate data. As opposed to studies investigating drug efficacy, conducting clinical trials to test strategies for lowering toxicity may be difficult because of financial support, physician perception, and public concern. Because some treatments for neuropathy are over-the-counter supplements (e.g., glutamine), obtaining financial support for a large, robust clinical trial may be difficult.
Management of Neuropathy in Cancer

Also, the balance between lowering or preventing neurologic toxicity and maintaining drug efficacy may be fine, because the 2 may be closely related. Randomized studies on preventative agents have been closed prematurely because of preliminary concerns on their negative impact on the efficacy of chemotherapy, although retrospective review did not support these concerns (see Prevention, page S-11).

Other clinical trials are still ongoing, but these studies will need to show reduced neurotoxicity without compromise of antineoplastic toxicity. This poses a major challenge, because large patient numbers are needed to provide sufficient power for proving non-inferiority. However, the persistent pattern of CIPN may present the opportunity to use a crossover design on intervention strategies, in which patients are randomized to 2 treatment sequences: placebo-agent or agent-placebo. Provided that carry-over effects are carefully considered, within-patient comparisons of crossovers can significantly enhance the statistical power by eliminating between-patient variation. This study approach has been effectively applied to polyneuropathic pain management, as well as cancer supportive care strategies.

Mechanisms of Neuropathy

Neurotoxicity Mechanisms of Chemotherapeutic and Biologic Agents

Neuropathy arises from damage to the peripheral nerves. Within the peripheral nervous system, the motor axons (nerve fibers) are large and myelinated, and the sensory and autonomic axons are mostly small and unmyelinated or thinly myelinated. The type of neuropathic symptom experienced depends on the type of nerve affected:

- Sensory nerves affect sensation, such as with painful paresthesia, dysesthesia, cold-sensitivity, tingling, numbness, alteration in vibration and proprioception, or a change in reflexes.
- Motor nerves affect muscles and motion, such as with muscle weakness.
- Autonomic nerves affect internal organs, such as with orthostatic hypotension, constipation, urinary retention, irregular heart rate, and sexual dysfunction.

Most neurotoxic drugs (taxanes and vinca alkaloids) used in chemotherapy cause axonal damage, a condition termed axonopathy. Primary nerve toxicity of the platinum drugs seems to occur at the dorsal root ganglion (DRG), resulting in neuronopathy. Small sensory fibers are affected early and most frequently by chemotherapeutic agents. Because these nerves have little capacity for regeneration, damage to them is responsible for the predominance of sensory symptoms found in CIPN. Also, the cell bodies of the peripheral sensory neurons are located in the DRG, where they are outside the protective blood-brain barrier and thus more vulnerable.

The DRG also has a rich supply of capillaries that are highly permeable to toxic compounds circulating in the blood. Motor nerves are generally less frequently or seriously affected by neurotoxic chemotherapy. Motor nerves that have survived a chemotherapeutic insult have the capacity for distal sprouting and reinnervation of muscle fibers that have lost their innervation. Clinically, this capacity for regeneration results in the recovery of the patient's strength and function. Autonomic nerves are also usually less sensitive to the effects of neurotoxic chemotherapy.

The exact mechanism of damage remains to be fully elucidated for each class of chemotherapy drugs, but various mechanisms based on in vitro and animal models have been proposed. The platinum compounds have been reported to accumulate in the DRG and exert direct damage to the DRG neurons, inducing DNA derangement, morphologic changes, and subsequent apoptosis. Cisplatin can also disrupt axonal microtubule growth that is essential for axonal transport. Studies suggest that the acute form of oxaliplatin toxicity may be associated with calcium chelation by oxalate released from the drug, adversely affecting ion channels and synaptic transmission. Like cisplatin, taxanes and vinca alkaloids have also been found to disrupt axonal transport via microtubule damage. Of note, vinca alkaloids are known to induce severe acute neurotoxicity in patients with Charcot-Marie-Tooth disease, a hereditary sensorimotor neuropathy. Correspondingly, the genetic mutations involved in this disorder are also linked to dysfunction in microtubules and axonal transport.

Among newer agents, a role in neuronal degeneration has been attributed to thalidomide. Bortezomib, a novel proteasome inhibitor, may induce neuronal injury via multiple mechanisms such as cytoskeletal change, mitochondrial disturbance, and disruption in tubulin polymerization.
The extent of nerve damage affects the distribution of symptoms. One useful classification of neuropathy is as follows:

- Mononeuropathy: damage to a single peripheral nerve
- Mononeuropathy multiplex: involvement of several isolated nerves
- Polyneuropathy: simultaneous malfunction of many peripheral nerves
- Autonomic neuropathy: damage to nerves affecting internal organs

CIPN is primarily polyneuropathic, with symmetric stocking-glove “dying back” distribution, with the earliest symptoms developing at the finger tips and toes (Figure 1). The length-dependent, distal pattern seems to indicate distal involvement of the longest peripheral axons, followed by progression of the symptoms proximally along the limbs as the neuropathy worsens. One explanation is that these longest fibers have the greatest surface area exposed to a CIPN drug and hence are subject to greater toxicity. Existing mononeuropathy such as median nerve damage found in carpal tunnel syndrome can worsen as CIPN polyneuropathy develops.

**Neuropathic Mechanisms From Other Conditions**

As previously discussed, PND is a rare condition that typically precedes tumor diagnosis and can lead to neuropathic symptoms in cancer patients. PND is thought to arise from autoimmune response directed against tumor antigens, which also cross-react with proteins normally found in the nervous system. A number of paraneoplastic antibodies have been characterized, many of which are commonly found in lung cancer patients (reviewed by Darnell and Posner81). Examples are the anti-CV2/CRMP5 and the anti-Hu antibodies associated with peripheral neuropathy and autonomic dysfunction. Detecting a paraneoplastic antibody can aid in the diagnosis of a previously unknown tumor, tumor recurrence, or rarely, a new second malignancy. In cancer patients with known PND, the most common etiology of CIPN, however, is still neurotoxic treatment.

A slightly greater incidence of other autoimmune neuropathies is found in cancer patients compared with the general population. These neuropathies include Guillain-Barré syndrome, an acute onset neuropathy that includes acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, acute motor sensory axonal neuropathy, and Miller Fisher syndrome. Chronic idiopathic demyelinating polyneuropathy and multifocal motor neuropathy can also be seen with greater frequency in cancer patients. In these cases, the body’s immune system mistargets the nerve tissues, causing inflammation or injury. Autoimmune mechanisms should be considered in HIV patients with cancer and transplant patients with neuromuscular symptoms, including neuropathy.

Diabetes is a common pre-existing comorbidity in cancer patients and is associated with a high incidence of peripheral neuropathy. The neuropathy-inducing mechanism of diabetes is still not fully understood, but it is widely attributed to hyperglycemia. Impaired glucose tolerance is seen in many non-diabetic cancer patients and can cause symptoms that are clinically similar to those of early diabetic neuropathy.

Systemic factors like weight loss predispose patients to focal compression neuropathies. The most common is peroneal nerve compression at the fibular head resulting in foot drop and sensory disturbance along the lateral aspect of the leg and over the foot. Patients with head and neck or gastrointestinal cancers are examples of patients who may experience significant weight loss within a short time period.

Patients with paraproteinemia such as monoclonal gammopathy of unknown significance; multiple myeloma; Waldenström’s macroglobulinemia; and polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome can develop neuropathy from various mechanisms. Patients may have antibodies against the nerve, develop secondary amyloid nerve deposition, or have circulating cryoglobulins causing vasculitis. However, even in these patients, neuropathy mostly is secondary to chemotoxicity.

**Evaluation**

CIPN is typically evaluated under 2 settings. First, it is commonly assessed during a clinical trial, either as part of the toxicity profile of a new antineoplastic drug or as the end point to determine the efficacy of a neuroprotective agent. Evaluation is also required during routine oncology practice, when patients complain of symptoms during the course of treatment. The following questions must be addressed:
• Are the symptoms due to neuropathy?
• If so, is the neuropathy a result of cancer treatment, cancer pathology, or other causes unrelated to cancer?
• Are the symptoms severe enough to require intervention?
• If so, what are the options for intervention or symptom management?
• Is modification or discontinuation of the present cancer treatment necessary?

To date, a gold standard for evaluating CIPN has not been defined. The assessment methods currently available include clinical evaluation (grading systems), objective testing, and patient questionnaires. However, standardization is lacking across these modalities. The largely subjective nature of pain and other neurogenic symptoms render objective measurement inherently difficult. Poor correlation between objective findings or physician evaluation and patient-reported symptom severity is frequently noted.

**Neurophysiologic and Other Objective Testing**

Neurophysiologic tests such as electromyography (EMG), nerve conduction studies (NCS), and quantitative sensory tests (QST) are objective quantitative assessments of the function of the peripheral nervous system. Limitations to objective testing include cost and the need for subspecialty expertise that may not be readily accessible at all medical sites. Some of these tests are also invasive, leading to low patient adherence. Also, reports of the added value to physician examination or patient questionnaires for CIPN have been inconsistent. In general, objective neurophysiologic findings correlate poorly with subjective reports by patients, with a tendency to underassess. For example, in a study of 38 cancer patients receiving second-line paclitaxel, 71% of patients reported symptoms of paresthesias and numbness in a questionnaire, but only 48% showed an increase in the vibration perception threshold (QST). Changes on EMG and NCS may also lag behind the onset of symptoms.

![Figure 1](image-url)  
Figure 1  Symptoms of chemotherapy-induced peripheral neuropathy.  
A series of laboratory and imaging tests is available to help evaluate for other possible causes of neuropathy, such as the paraneoplastic panel (anti-Hu, anti-Yo, anti-Mag) for PND diagnosis, blood tests for metabolic or nutritional deficiency-mediated neuropathy, or MRI for identifying compressive radiculopathy. However, these are usually only conducted on outlier cases in the cancer setting. In-office skin biopsy at proximal and distal anatomic sites is performed for density measurement of intra-epidermal nerve fibers to evaluate small fiber neuropathies. Although highly specific, it has low sensitivity and the same limitations as neurophysiological testing (cost, pain, inadequate correlation with patient reports).

**Clinical Assessment**

As opposed to specialized neurophysiologic testing, clinical assessment (history and physical examination) is performed by the treating oncologist and typically the first-line evaluation of CIPN. Patient history should include associated comorbidity, personal and family history of neuropathy, alcohol use and other toxic exposures, and any CIPN experienced during previous treatment. The temporal profile should be described in detail (regimen dosage, duration, schedule, coexisting), as well as the characteristics and distribution of signs and symptoms. Physical examination should describe clinical features of the neuropathy, such as sensory abnormalities, deep tendon reflex dysfunction, motor weakness, pain characteristics, autonomic symptoms, and most importantly, functional impairment. For individuals with pre-existing or hereditary neuropathy, related musculoskeletal findings should be documented. Such abnormalities can include foot deformities such as high arches, flat feet, hammer toes (deformity of the proximal interphalangeal joint of the second, third, or fourth toe causing them to be permanently bent).

A number of physician-based grading systems have been developed for CIPN assessment. The most widely used are the NCI-CTCAE, Ajani Sensory, WHO, and ECOG systems (Table 2).56–89 These systems grade CIPN from grade 0 (normal) to 4 (severe) or 5 (death). However, variability is apparent among examiners and different scoring systems. In a key study conducted by Postma et al.,90 2 neurologists independently rated the severity of CIPN in 37 patients using the NCIC-CTCAE (adapted from the NCI-CTC), WHO, ECOG, and Ajani scales. In 80% of the cases, the neurologists disagreed on at least one scale; complete agreement on all 4 scales was noted in only 20% of patients. Interobserver agreement ranged from 46% (NCIC-CTC) to 84% (WHO), and interscale agreement for the dichotomy grade 2 and under; grade 3 varied from 68% (WHO and NCIC-CTCAE) to 100% (WHO and ECOG). This study highlights the disparity in interpretation among physicians, as well as the substantial variation in grading when using different grading systems.

The significant problem of variability is in part caused by the lack of clearly defined evaluation parameters. For instance, the phrase “interfering with function but not interfering with activities of daily living” in grade 2 of the NCI-CTCAE specifies neither the function nor activity and thus is open to interpretation. Other criticisms include mixing of objective parameters (e.g., loss of reflex) with subjective symptoms (e.g., paresthesias), lack of pain assessment, and failure to account for chronic toxicity and changes in symptoms.89 More recently, a newer tool, Total Neuropathy Score (TNS),91 was developed that was reported to be more sensitive than the NCI-CTCAE in detecting changes in CIPN.

**Patient-Based Evaluation**

As previously discussed, underestimation and underreporting of CIPN using physician-based methods is substantial.57–59 Neuropathic symptoms such as pain and paresthesias are predominantly subjective, and individuals may have different thresholds of tolerance for these symptoms. Direct input from the patient is therefore critical in the evaluation, because the requirement for intervention is largely based on patient preference. Patient-based instruments that have been developed to address this need include the Functional Assessment of Cancer Therapy (FACT)/Gynecology Oncology Group-Neurotoxicity,94 FACT-Taxane,95 and Patient Neurotoxicity Questionnaire (PNQ).1 These are self-administered questionnaires designed to determine the level and incidence of clinically significant functional impairment resulting from CIPN.

**Recommendations**

For routine oncology practice, the Task Force panel strongly encourages physicians to actively query cancer patients on signs and symptoms of neuropathy. Before neurotoxic therapy is administered, a baseline assessment should be performed and recorded. Iden-
Identifying pre-existing conditions that may predispose patients to and potentially exacerbate CIPN is imperative. Of special concern are patients with hereditary motor and sensory neuropathies, such as Charcot-Marie-Tooth disease, who may develop severe neuropathic paralysis when receiving vincristine. Routine assessment should continue during therapy. Because most cases of CIPN progress with dose accumulation, early report of mild cases is important for detecting the onset of neuropathy during continuous monitoring. For a list of diagnostic features of CIPN that distinguishes it from other types of neuropathy, see Chemotherapy-Induced Peripheral Neuropathy (page S-2).

The main goal of routine clinical assessment is to determine whether the patient is experiencing...
significant neuropathic symptoms that require intervention. For this purpose, the use of grading systems is helpful but not sufficient alone. In particular, pain is a major symptom that is not well addressed by existing scales. The panel suggests the following pain assessment tools commonly used under other clinical settings: Brief Pain Inventory, Neuropathic Pain Scale, and Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS). Whether to intervene with the neuropathic symptoms that arise depends on patient preference and the medical judgment of the physician.

Table 3 lists recommendations by the NCCN Task Force panel on the key points to include during assessment of neuropathy on a cancer patient. In addition to a history and physical examination, functional assessment is critical. Simple skill tests and questions about activities of daily living provide important information. Physicians can also refer to existing patient questionnaires.

Panelists agree that referral to a specialist can also be helpful. This may be a neurologist or physiatrist (specialist in physical medicine and rehabilitation) experienced in managing neuromuscular disorders in the cancer setting. When pain is a predominant issue, referral to a supportive care or pain management specialist may improve overall patient management. The exact point of referral will depend on physician discretion and the infrastructure of individual medical centers, but it is important that such a system be in place. In general, oncologists should consider referral when the patient case is out of their usual clinical experience, such as when a patient has atypical signs, severe symptoms, or underlying neuropathic disorders.

Specialists can help delineate the neuropathic etiology, which may affect decisions about cancer treatment, suggest treatment, or point to resources for patient support and rehabilitation (see Management of Functional Deficits, page S-17). However, the panel emphasized that specialist scheduling should be in parallel with ongoing oncologist visits so that logistics do not delay appropriate antineoplastic treatment. Communication between the treating physician and specialist is essential.

Objective neurophysiologic testing is not sufficiently reliable to be used alone for decision making. But such testing may be used as an adjunct to clinical assessment for confirming or ruling out a diagnosis. Similarly, the need for additional laboratory testing, imaging, or biopsying depends on the initial clinical assessment. The decision to order these tests is usually made by the specialist.

For clinical trials, multimodality assessment is preferable. Simple QST like the Von Frey or Neuropen may be easier for standardization than tests that require extensive setup or equipment. Given the high variability of commonly used physician-based scoring systems, multicenter studies must reach a consensus on the grading scale as well as interpretation of the chosen scale. As pointed out by panelists, pain assessment and functional impairment are critical endpoints, and the integration of pain scales (Brief Pain Inventory, LANSS, Neuropathic Pain Scale), patient-based questionnaires (FACT, PNQ) and skill tests (timed pellet retrieval, pegboard test) is strongly encouraged.

**Prevention**

Many agents have been proposed for preventing neuropathy caused by antineoplastic drugs. The mechanisms by which most of these drugs might minimize neuropathy are based on limited preclinical data and informed opinion. Most of these agents have been studied in clinical trials with designs inadequate for definitive assessment of the impact on neuropathy. A few have been evaluated in randomized controlled trials. Most have been assessed during platinum-based chemotherapy. Table 4 lists these agents, the proposed mechanism for preventing CIPN, and findings from clinical trials.

Vitamin E may mitigate neuropathy associated with platinum-based chemotherapy. Three small, open-labeled studies randomized 30 to 47 cancer patients receiving chemotherapy mostly consisting of cisplatin to vitamin E or control. The active arms were consistently associated with a lower incidence of CIPN (21%–31%) compared with the control arm (69%–86%), with statistical significance (P < .03). The severity of neuropathy as measured by toxicity scores was also reduced.

A double-blinded, randomized, placebo-controlled study of 81 patients undergoing cisplatin therapy is ongoing. Interim analysis of the first 50 patients showed a significantly lower median toxicity score in the supplement group. Because vitamin E is an antioxidant, concerns have been raised.
about the possibility that it may suppress chemotherapy efficacy by interfering with the oxidative breakdown of DNA and membranes of cancer cells. Preclinical models have shown no difference in cisplatin-induced tumor inhibition with or without vitamin E.\textsuperscript{124,125} In a randomized study of 136 lung cancer patients receiving paclitaxel and carboplatin, multiple high-dose antioxidant supplementation including vitamin E affected neither the response rate nor survival.\textsuperscript{123} These results are reassuring, but a well-designed, adequately-powered trial to confirm the safety of vitamin E is important before its general adoption.

Intravenous administration of calcium and magnesium (CaMg) has been proposed as prophylaxis against neurologic damage induced by oxaliplatin, on the basis that heightened extracellular calcium could facilitate closing of sodium channels, thereby decreasing the hyperexcitability of neurons exposed to oxaliplatin.\textsuperscript{124} Two concurrent randomized controlled trials, N04C7 and CONcePT, were initiated to test the effect of CaMg on oxaliplatin-related neuropathy. Both trials were terminated after CONcePT investigators reported diminished response to chemotherapy in the CaMg arm.\textsuperscript{125} After study termination, however, a subsequent independent radiology review suggested the opposite finding with respect to tumor response.\textsuperscript{121,126}

Despite early termination, the N04C7 study revealed a reduction in CIPN incidence in the active arm.\textsuperscript{106} Gamelin et al.\textsuperscript{127} released an interim report on their multicenter, double-blind trial (Neuroxa) randomizing patients on the FOLFOX4 regimen. There was no difference in the response or survival rates between the arms, but significantly lower frequency and severity of neuropathy were seen in one group (blind not yet broken). Future updates should clarify the effectiveness and safety of CaMg.

Despite various rationales for their evaluation, other drugs such as amifostine, nimodipine, Org 2766, and rhuLIF have all failed to show clinical benefit in randomized trials. Recently, new agents, including acetyl-L-carnitine, alpha lipoic acid, and vitamin B12/B6, have entered phase III randomized clinical testing.

**Conclusions**

Although several agents have shown potentially encouraging results as mitigators of neuropathy, current data are inadequate to recommend any for

### Table 3  Key Points to Report During Clinical Assessment of CIPN

<table>
<thead>
<tr>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Personal history of neuropathy and CIPN from previous cancer treatment</td>
</tr>
<tr>
<td>• Personal and family history of hereditary neuropathy (patients with Charcot-Marie Tooth disease should avoid vincristine-based chemotherapy)</td>
</tr>
<tr>
<td>• Related comorbid conditions (e.g., diabetes, HIV, Guillain-Barré syndrome, CIDP, radiculopathy)</td>
</tr>
<tr>
<td>• Alcohol use</td>
</tr>
<tr>
<td>• Temporal profile: regimen dosage, duration, schedule, “coasting” effects</td>
</tr>
<tr>
<td>• Symptoms</td>
</tr>
<tr>
<td>• Type: sensory, motor, or autonomic</td>
</tr>
<tr>
<td>• Distribution: distal symmetric or asymmetric</td>
</tr>
<tr>
<td>• Severity</td>
</tr>
<tr>
<td>• Pain assessment: BPI, LANSS, NPS</td>
</tr>
<tr>
<td>• Time course of CIPN, including onset and resolution of symptoms</td>
</tr>
<tr>
<td>• Treatment delays or discontinuation related to CIPN</td>
</tr>
</tbody>
</table>

### Physical Examination |

| Sensory assessment: light touch, vibration, proprioception, pin-prick, temperature |
| Deep tendon reflex: presence, absence, diminishment |
| Motor weakness |
| Autonomic symptoms (e.g., constipation, orthostatic hypotension, urinary dysfunction, sexual dysfunction) |
| Related musculoskeletal abnormalities (e.g., hammertoes, high or flattened arches) |

### Sample Questions for Patient |

| • Do you feel numbness or tingling in your hands or feet? |
| • Do you feel pain in your hands and feet? (Rate it on a scale of 0 to 10.) |
| • Do you feel like having gloves and stockings on? |
| • Do these sensations bother you? Are they getting worse? |
| • Do you feel weakness in your arms and legs? |
| • Do you drop things often? |
| • Have you fallen recently? |
| • Do you have difficulty walking or climbing stairs? |
| • Do these sensations interfere with your work or daily activities? |

### Examples of Functional Assessment Skill Tests |

| • Getting up and straight-line walking (observe gait and balance) |
| • Name writing |
| • Buttoning |
| • Timed pellet retrieval (for clinical trials) |
| • Pegboard test (for clinical trials) |

Abbreviations: BPI, Brief Pain Inventory; CIDP, chronic idiopathic demyelinating polyneuropathy; CIPN, chemotherapy-induced peripheral neuropathy; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale; NPS, Neuropathic Pain Scale.
Recommendations for cancer patients is unclear. Larger randomized controlled studies specifically in cancer are needed to delineate the safety and efficacy of neuropathy prophylaxis, although these may be met with several challenges, as discussed previously.

The panel was concerned by the inconsistency of end points used among the various trials examining neuropathy and potential interventions. Frequently, discordance is apparent between symptom reports and objective measures, and satisfactory neuropathy evaluation tools are currently lacking, as discussed previously. Panelists agreed that multimodal measurement of functionality is of primary importance and the incorporation of simple skill tests (e.g., the pegboard test) will add valuable information at a relatively low cost.

### Table 4 Proposed Agents for Preventing CIPN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Findings From Randomized Controlled Trials (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agents with Positive Findings in Randomized Controlled Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Antioxidant/minimizes neuronal damage</td>
<td>CIPN incidence and severity reduced (30-47)&lt;sup&gt;102-104&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CIPN severity reduced (81)&lt;sup&gt;105&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ongoing trial: NCT00363129*</td>
</tr>
<tr>
<td>Ca&lt;sup&gt;++&lt;/sup&gt;/Mg&lt;sup&gt;++&lt;/sup&gt;</td>
<td>Facilitates Na channel function; binds oxalate (metabolite of oxaliplatin)</td>
<td>CIPN incidence reduced (104)&lt;sup&gt;106&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Upregulation of nerve growth factor</td>
<td>CIPN incidence reduced (86)&lt;sup&gt;107&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glutathione</td>
<td>Hampers accumulation of platinum adducts in DRG</td>
<td>CIPN incidence reduced/trend towards reduction (50-151)&lt;sup&gt;108-110&lt;/sup&gt;</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Antioxidant; increases blood concentrations of glutathione</td>
<td>Incidence of grade 2-4 neuropathy reduced (14)&lt;sup&gt;111&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Inhibits high-frequency firing of nerves; modulates ion channels</td>
<td>Neurpathy incidence reduced (32)&lt;sup&gt;112&lt;/sup&gt;</td>
</tr>
<tr>
<td>Xaliproden</td>
<td>Non-peptide neurotrophic agent</td>
<td>Shift of CIPN from grade 3 to grade 2 (649)&lt;sup&gt;113&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ongoing trial: NCT00603577*</td>
</tr>
<tr>
<td><strong>Agents With Negative Findings in Randomized Controlled Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amifostine</td>
<td>Detoxifies chemotherapy; facilitates DNA repair</td>
<td>Not effective (66)&lt;sup&gt;114&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improvement on NCI-CTC scale but not on patient questionnaire (72)&lt;sup&gt;115&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Calcium channel antagonist</td>
<td>Not effective; randomized trial closed early (51)&lt;sup&gt;116&lt;/sup&gt;</td>
</tr>
<tr>
<td>Org 2766</td>
<td>Nerve growth factor family, adrenocorticotrophic hormone analog</td>
<td>Vibration perception maintained (55)&lt;sup&gt;117&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not effective (150-196)&lt;sup&gt;118,119&lt;/sup&gt;</td>
</tr>
<tr>
<td>rhuLIF</td>
<td>Neuroprotective cytokine</td>
<td>Not effective (117)&lt;sup&gt;120&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Additional Agents Being Tested in Ongoing Phase III Randomized Controlled Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12/B6</td>
<td>Essential for nerve function</td>
<td>Ongoing trial: NCT00659269*</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>Oxidation of free fatty acids/nerve regeneration</td>
<td>New trial: NCT00775645*</td>
</tr>
<tr>
<td>Alpha lipoic acid</td>
<td>Antioxidant</td>
<td>Ongoing trial: NCT00705029*</td>
</tr>
</tbody>
</table>

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; DRG, dorsal root ganglion; NCI-CTC, National Cancer Institute Common Toxicity Criteria. *ClinicalTrials.gov identification number.
Treatment

Non-Cancer–Related Neuropathy

Treatment of neuropathy in cancer patients remains a challenge and depends on etiology. As discussed, a main complication is that an individual patient may experience neuropathic symptoms caused by a combination of factors. Distinguishing CIPN from other types of neuropathy is important in deciding whether the antineoplastic treatment needs to be modified. Damage to the peripheral nervous system at other levels, including the nerve root and plexus, may mimic peripheral neuropathy. Care should be taken in evaluation and exclusion of such disorders, particularly in patients with a history of degenerative spine disease or radiation therapy that affects the nerve root or plexus. Identifying underlying neuropathy is essential, because specific treatment or management strategies are available for certain non-cancer–related neuropathies:

- **Hereditary:** cancer patients with Charcot-Marie-Tooth disease should avoid vincristine-based chemotherapy

- **Diabetes:** control of glucose level and weight, exercise, and pain relief can be helpful

- **Alcohol:** avoiding alcohol, improving nutrition (vitamin supplement), and pain relief can be helpful

- **HIV:** controlling HIV and selecting medication that has a low risk of contributing to neuropathy

- **Guillain-Barré syndrome:** intravenous immunoglobulin (IVIg) and apheresis

- **Chronic idiopathic demyelinating polyneuropathy (CIDP):** steroids, intravenous immunoglobulin, and apheresis

- **Mononeuropathy (i.e., median mononeuropathy causing carpal tunnel syndrome, ulnar mononeuropathy):** resting hand splints, physical or occupational therapy, corticosteroid injection, surgical decompression (it should be noted that surgical decompression in patients on active antineoplastic treatment was thought to be relatively contraindicated by the panel)

Cancer-Related Neuropathy

In most instances, control of the tumor remains a priority for stabilizing or improving cancer-related neurophathic conditions. Surgery remains the most efficient way to relieve symptoms, particularly when the neuropathy is the result of direct tumor compression. Radiation therapy and chemotherapy may also be of benefit when treating tumors responsive to these therapeutic modalities. Steroids or intravenous immunoglobulin may be effective against specific subtypes of PND such as Lambert-Eaton myasthenic syndrome and paraneoplastic dermatomyositis.

Randomized trials have shown brief efficacy of intravenous immunoglobulin in treating anti-MAG neuropathy. Current treatment schema also includes rituximab and apheresis. For the rare polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome, surgery and radiation against the plasmaproliferative disorder is the mainstay of treatment; steroids are also effective.

CIPN

To date, no approved effective treatment is available for CIPN, although a number of medications are useful for pain control (see subsequent sections). Because CIPN symptoms may progress with cumulative exposure, close monitoring is necessary during chemotherapy. In severe cases, dose reduction or treatment discontinuation may be indicated at the discretion of the treating oncologist, but this must be weighed against the oncologic risks.

Symptom Management: Pain Medications

Various pharmacologic agents have been tested in symptom control trials to alleviate established neuropathy. Drugs that have been approved by the FDA have been so based on their efficacy in reducing pain intensity for other types of neuropathic pain disorders, mainly diabetic neuropathy and post-herpetic neuralgia. Most clinical trials on the use of other drugs to moderate CIPN have failed to yield positive findings, although results from 2 recent studies are more encouraging. To date, no agent has been approved specifically for treating CIPN. Table 5 lists the medications that are currently being used off-label to relieve the positive symptoms of CIPN (pain, paresthesias, dysesthesias, allodynia). It should be noted that none of these agents are effective in the treatment of negative neuropathic symptoms such as weakness or the loss of sensory modalities, including light touch or proprioception. Many of these agents should be administered at a low starting dose and slowly titrated to the dose that confers the best efficacy with limited side effects. Specifications for administration and side effects are listed. Readers can also refer to the NCCN Clinical
of pregabalin (NCT00380874) in advanced colorectal cancer patients was terminated due to insufficient conditional power to detect differences. Nonetheless, panelists reported from their clinical experience that both pregabalin and gabapentin may be helpful in treating pain associated with CIPN. Compared with gabapentin, pregabalin has similar and perhaps milder side effects, faster onset of action, better absorption, and less need for dosage titration.

Local Anesthetics: The 5% lidocaine patch has the advantage of minimal side effects (local rash) and ease of administration. It has been shown to alleviate allodynia (a form of dysesthesia) mainly in patients with post-herpetic neuralgia, but has not been shown to have a significant impact on pain intensity in cancer patients with postsurgical pain.

Practice Guidelines in Oncology: Adult Cancer Pain (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org) for pain management strategies in cancer patients.

Antiepileptic Drugs: Gabapentin is an anti-epileptic drug widely used for neuropathic pain. In randomized controlled trials involving mixed populations, gabapentin was found to relieve pain and improve sleep, mood, and quality of life. However, in a double-blinded, controlled, crossover trial (n = 115) gabapentin was no better than placebo in reducing CIPN.

Pregabalin has the same mechanism of action as gabapentin and is approved for the treatment of diabetic neuropathy and post-herpetic neuralgia. Its efficacy in reducing neuropathic pain has been shown in 6 randomized trials. A phase IV trial of pregabalin (NCT00380874) in advanced colorectal cancer patients was terminated due to insufficient conditional power to detect differences. Nonetheless, panelists reported from their clinical experience that both pregabalin and gabapentin may be helpful in treating pain associated with CIPN. Compared with gabapentin, pregabalin has similar and perhaps milder side effects, faster onset of action, better absorption, and less need for dosage titration.

Local Anesthetics: The 5% lidocaine patch has the advantage of minimal side effects (local rash) and ease of administration. It has been shown to alleviate allodynia (a form of dysesthesia) mainly in patients with post-herpetic neuralgia, but has not been shown to have a significant impact on pain intensity in cancer patients with postsurgical pain.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Titration</th>
<th>Maximum Dose</th>
<th>Duration of Adequate Trial</th>
<th>Potential Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>20–30 mg/d</td>
<td>No evidence that higher dose is more effective</td>
<td>120 mg/d</td>
<td>2 wk</td>
<td>Nausea, xerostomia, constipation, diarrhea</td>
</tr>
<tr>
<td>Gabapentin*</td>
<td>100–300 mg nightly or 100–300 mg 3 times/d</td>
<td>Increase by 100–300 mg 3 times/day, every 1–7 days</td>
<td>3600 mg (depending on absorption)</td>
<td>1–2 wk at max tolerated dose</td>
<td>Somnolence, dizziness, GI symptoms, mild edema, cognitive impairment (elderly), exacerbation of gait problems</td>
</tr>
<tr>
<td>5% Lidocaine patch</td>
<td>Maximum of 3 patches daily</td>
<td>Non-applicable</td>
<td>3 patches</td>
<td>2 wk</td>
<td>Rash/erythema</td>
</tr>
<tr>
<td>Opioids (oxycodeone, morphine, methadone)</td>
<td>5–15 mg every 4 h</td>
<td>Convert to long-acting after 1 wk, titrate based on breakthrough use</td>
<td>No ceiling effect</td>
<td>4–6 wk</td>
<td>Constipation, nausea, vomiting (self-limited), sedation, confusion, respiratory depression</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>25–50 mg 3 times/d</td>
<td>Increase by 50 mg/dose after 1 wk</td>
<td>200 mg 3 times/d</td>
<td>Unclear (likely 2–4 wk)</td>
<td>Dizziness, somnolence, xerostomia, edema, blurred vision, decreased concentration</td>
</tr>
<tr>
<td>Tramadol</td>
<td>50 mg 1–2/d</td>
<td>Increase by 50–100 mg/d, individual doses every 3–7 days</td>
<td>400 mg/d (100 mg 4 times/d); elderly 300 mg/d</td>
<td>4 wk</td>
<td>Dizziness, constipation, nausea, somnolence, orthostatic hypotension, increased risk of seizure, serotonin syndrome</td>
</tr>
<tr>
<td>Tricyclic antidepressants (amitriptyline,* nortriptyline,* desipramine)</td>
<td>Starting dose: 10-25 mg nightly</td>
<td>Increase by 10-25 mg every 3-7 days</td>
<td>75–150 mg; may increase if blood level of drug plus metabolite &lt;100 ng/mL</td>
<td>6-8 wk; 1-2 wk at max dose</td>
<td>Cardiovascular disease (needs screening), anticholinergic effects, interact with drugs metabolized by cytochrome P450 2D6 (e.g., cimetidine, phenothiazine)</td>
</tr>
</tbody>
</table>

*Negative results in randomized controlled clinical trials on chemotherapy-induced peripheral neuropathy
Antidepressants: Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) that is effective in reducing pain in patients with diabetic neuropathy.\textsuperscript{153–155} It has the advantage of being fast-acting, with rapid onset of action within the first few doses. However, duloxetine should be avoided in patients on tamoxifen because it will decrease the concentration of endoxifen, an active metabolite of tamoxifen. As a serotonin reuptake inhibitor, duloxetine is relatively contraindicated when used with other drugs that affect serotonin reuptake, including the selective serotonin reuptake inhibitors, tricyclic antidepressants, tramadol, and triptans commonly used to treat migraines for fear of causing the potentially fatal serotonin syndrome. A randomized, placebo-controlled trial of duloxetine in cancer patients with CIPN is ongoing (NCT00489411). Another SNRI, venlafaxine, has recently been reported to reduce the incidence of acute oxaliplatin-induced neuropathic pain compared with placebo (35% vs. 76%) in a small trial of 54 patients.\textsuperscript{139}

Tricyclic antidepressants (TCAs; amitriptyline, nortriptyline, and desipramine) are FDA-approved for relieving symptoms of depression, not neuropathic pain. Despite this, they were the first class of nonopioid medications to gain widespread use in the treatment of neuropathic pain, based on benefits seen primarily in diabetic patients.\textsuperscript{156} Unfortunately, studies of these agents are limited by substantial side effects (high drop-out rates) and their pharmacologic interactions with drugs metabolized by cytochrome P450 2D6. Their potential negative impact on cardiovascular function necessitates screening, especially in elderly patients. Despite TCA’s efficacy on diabetic neuropathy, 2 randomized, placebo-controlled trials (n = 44 and 51, respectively) of amitriptyline and nortriptyline yielded negative results in patients with CIPN.\textsuperscript{134,135} Given these limitations, TCAs are not typically used as a first-line pain medication for CIPN. More recently, a topical gel formulation BAK-PLO (baclofen, amitriptyline, and ketamine in pluronic lecithin organogel) moderately improved CIPN symptoms in a randomized trial of 208 cancer patients.\textsuperscript{138}

Opioids: Tramadol is a centrally acting analgesic. It is often considered a mild opioid but has other analgesic properties and may be considered a novel agent. It has shown efficacy in relieving painful diabetic neuropathy and improving patients’ quality of life.\textsuperscript{157,158} The maximum dose is 400 mg per day for most adults and 300 mg per day for elderly patients.

The opioids morphine and oxycodone provide analgesia and lessened sleep interference for diabetic neuropathy when used alone or in combination with gabapentin.\textsuperscript{141,159–161} Task Force members pointed out that although the opioid methadone is used frequently, its use is complicated by a very long half-life, effect on QT intervals, and many drug–drug interactions that can result in serious adverse events. Current recommendations suggest that only clinicians with experience administering methadone should prescribe this medication. Other opioids (tramadol, morphine, oxycodone) that have been tested for neuropathy may be considered safer alternatives in treating CIPN.

Other medications that have been studied include lamotrigine,\textsuperscript{136} selective serotonin reuptake inhibitors, mexiletine, 0.75% capsaicin, and intravenous lidocaine. However, these are not recommended for routine use because of mixed results or safety issues.

Recommendations: Currently, the general approach to pain medication for CIPN is to choose an agent based on the clinician’s experience and expectation of efficacy and safety, and titrate that agent to the maximal tolerated dose. If a single agent is effective, then it should be continued. If a single agent confers partial but incomplete benefit, then a second agent with a different mechanism of action should be chosen and added. If the first agent is ineffective or poorly tolerated, then it should be discontinued and another agent chosen and titrated. Often many agents will be needed for adequate analgesia. Panelists agreed that the clinical context of the treatment will determine the choice of medication. For example, a fast-acting agent with low risk of nausea will be most suitable for a patient going through active adjuvant chemotherapy before surgery. Unfortunately, there is inadequate evidence on the best order of administration and combination. Two randomized, double-blinded trials in 41 to 338 patients, primarily with diabetic neuropathy, showed more effective pain reduction with the combination of an opioid (morphine or oxycodone) and gabapentin compared with gabapentin alone, with little exacerbation of side effects.\textsuperscript{141,160}
Symptom Management: Neurostimulation Therapies

Medication is often insufficient to mitigate neuropathic pain, and alternative nonpharmacological therapies have been investigated. In particular, electrical stimulation therapies, typically administered by a specialist, have elicited some benefits. They are generally considered reversible, although they vary widely in their degree of invasiveness. These neurostimulation techniques are generally based on the gate control theory proposed by Melzack and Wall, they are designed to relieve pain by somatotopically "masking" the affected area with non-painful stimulation of A-beta afferent fibers, thereby blocking out the painful stimuli. Hence these modalities are seldom effective towards patients with deafferented nerves leading to numbness or tingling. The European Federation of Neurological Forces (EFNS) recently produced a detailed review and recommendations on these techniques for neuropathic pain. As with pain medications, most evidence supporting neurostimulation came from studies on diabetic or other types of neuropathy. Data on CIPN are anecdotal.

Spinal cord stimulation (SCS) involves the surgical placement of electrodes into the epidural space that can send non-noxious electrical stimulation across the spine to displace the painful sensation. SCS has been shown to provide good pain relief in small case series of patients with refractory CIPN (n = 2–4) and other types of neuropathy (n = 6–19). Long-term effects up to 8 years are reported. Of note, SCS is an invasive technique that includes the risks and costs of surgery, although a temporary lead is typically tested for a trial period before permanent implantation. There were initial concerns that cancer patients with SCS may suffer neurologic injury during an MRI, but published case reports as well as panelists’ experience indicate that it is safe to perform MRI with the SCS temporarily turned off.

Similar techniques include motor cortex stimulation and deep brain stimulation, which require surgical implantation into the brain. These procedures are highly invasive and have little evidence to support their use for treating neuropathic pain. High frequency (5–20 Hz) repetitive transcranial magnetic stimulation is a noninvasive technique that applies the coil of a magnetic stimulator above the scalp. There is evidence that it alleviates pain for post-stroke central pain syndromes, but its effects are short-lived and moderate.

Electrical nerve stimulation, either transcutaneous (TENS) or percutaneous, originally developed in the 1960s for treating nociceptive and musculoskeletal syndromes, uses portable skin patches to pass electrical current through the cutaneous tissues. Nine small trials involving an aggregate of approximately 200 patients with neuropathic pain generally associate TENS with a positive effect on pain control (reviewed by Cruccu et al.). One randomized study involving 41 diabetic patients showed a higher response rate with high-frequency TENS (69%) than with TENS (25%). However, the study had no placebo. Other studies have shown that acupuncture-like low frequency TENS is better than sham stimulations.

An emerging technique called anodyne therapy uses monochromatic near-infrared photo energy to increase circulation to nerves and reduce pain. Small studies (n = 21–27) have shown a benefit for diabetic patients, but a strong placebo effect was present in 2 randomized, sham-controlled trials. Several panelists noted that burns are a potential risk in patients with sensory deficits and that no efficacy studies have been performed in oncology patients.

Recommendations: Current literature is inconclusive on the benefits of neurostimulation in treating CIPN, and more rigorous studies are needed. Despite a lack of evidence, panelists generally agreed that TENS can be a helpful adjuvant therapy for CIPN patients with contraindications to or for whom pain medication is ineffective, considering its ease of application, reversibility, and relatively low cost.

Complementary and Alternative Medicine Therapies

According to the National Center for Complementary and Alternative medicine, complementary and alternative medicine (CAM) is a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine. CAM therapies have achieved widespread use among patients with neurologic disorders. A questionnaire-based study found that 77 of 180 (43%) patients with peripheral neuropathy used CAM, such as megavitamins (35%) and acupuncture (30%). In another report of 450 patients, pa-
tients indicated massage (35%), meditation (18%), and acupuncture (10%) as common self-care strategies for HIV-related peripheral neuropathy. Clinical studies investigating natural products as prophylactics for neuropathy and neurostimulation techniques for pain management have been discussed in previous sections. Among other CAM approaches, most research focused on acupuncture. Originally from Chinese traditional medicine, modern acupuncture is based on the theory that insertion and manipulation of a needle at specific acupuncture points in the body induces signals in afferent nerves that subsequently regulate spinal signal transmission and neural pain perception. This theory is supported by preclinical studies and animal models (reviewed by Wang et al.).

Alimi et al. randomized 90 cancer patients with mainly neuropathic pain to auricular acupuncture and 2 placebo groups (acupuncture or auricular seeds at placebo points). At 2 months, pain intensity decreased by 36% from baseline with acupuncture versus 2% with placebo (P < .0001). Another randomized controlled trial enrolling 250 patients with HIV-related neuropathy found that both acupuncture and amitriptyline reduced symptoms, with a favorable trend over placebo that did not reach statistical significance. A non-randomized trial of 47 patients with idiopathic neuropathy reported improvement both in symptoms and objective NCS measurements for 76% of patients receiving acupuncture compared with only 15% receiving best medical care. For CIPN, only one pilot, single-arm, prospective case series of 5 patients was performed. The pain scores were lowered in all patients (average 8 points reduced to average 3 points) after two 6-week courses of acupuncture.

Evidence is scarce on the efficacy of other CAM therapies on neuropathic symptoms. Case series of successful treatment of neuropathic pain by biofeedback have been reported, but no data from prospective trials are available. Dietary supplements have also been studied for prevention and treatment of neuropathy. They include alpha-lipoic acid, acetyl-L-carnitine, benfotiamine, methylcobalamin, topical capsaicin, vitamin E, glutathione, folate, pyridoxine, biotin, myo-inositol, omega-3 and -6 fatty acids, L-arginine, L-glutamine, taurine, N-acetylcysteine, zinc, magnesium, chromium, and St. John’s wort.

Conclusions: The increasingly widespread use of CAM therapies among patients and the current paucity of evidence on their safety and efficacy in treating CIPN raise the need for more controlled, sufficiently powered studies. Acupuncture is a more promising approach supported by scientific plausibility, although the technique lacks standardization. As with TENS, it is noninvasive and relatively inexpensive, and it may be considered as an adjunct option in treating patients with medication-resistant CIPN. Several natural products available to the public as dietary supplements also showed promise, although their definitive efficacy has not been established.

Management of Functional Deficits

Cancer patients with CIPN often present with significant functional deficits especially as their condition worsens. These deficits may include decreased balance, gait abnormalities, muscle weakness, and sensory loss, which can lead to an increased fall risk, difficulties in performing activities of daily living, safety concerns, and diminished participation. Rehabilitation specialists, particularly physical and occupational therapists, are uniquely qualified to assess patients with CIPN and provide interventional strategies (both remedial and compensatory) to help patients either reverse or safely deal with these interrelated deficits.

The brain requires sensory and proprioceptive information from the periphery to maintain balance; therefore, the sensory losses associated with CIPN can result in balance deficits. For example, Visovsky and Daly recorded a slight decline of 12% in balance over the course of 12-week carboplatin treatment in cancer patients. Similarly, Wampler et al. significantly correlated increasing balance deficits with increasing CIPN severity in 20 breast cancer patients who had received taxane chemotherapy.

Clinical assessments of balance can be made using simple tests such as the Single Limb Stance Test (time patient can stand on one leg), Tandem Standing Test (time patient can stand heel to toe), or the Timed Up and Go test (the patient stands up, walks 10 feet, returns and sits down), or more complex tests such as the Berg balance test or the Rhomberg balance test. Computer-based biomechanical analysis of balance, which provides quantitative assessment, is increasingly available for use in a clinical setting. Questionnaires like the Activities-Specific Balance Confidence Scale are also used clinically to evaluate balance.
Therapeutic interventions aimed at improving balance typically involve progressive task training starting with static standing activities (firm and hard surfaces) and then advancing first to static standing coupled with simple manipulation activities (e.g., holding a glass of water, passing a basketball), then to walking (different surfaces) and finally to walking coupled with simple manipulation activities. Modification or elimination of visual input can also be included to make these tasks more demanding. In a case report discussing a patient with stage III breast cancer with docetaxel-associated neuropathy, such a program (45–60 minutes per session, 2 times per week, 4 weeks total) improved the patient’s sense of balance.

Gait training and lower extremity strengthening exercises are important therapeutic activities that improve balance, as shown by a study (n = 20) of diabetic patients undergoing intense daily strengthening exercises (e.g., toe raises, heel raises, wall slides). Compared with a control exercise regimen, these strengthening exercise significantly enhanced balance. Assistive devices including canes, walkers, wheelchairs, and ankle-foot orthoses may also be recommended, less to reverse this deficit and more to compensate for it.

Although the incidence of falls in patients with CIPN has not been reported, the risk for falls is 5 times greater in older patients with peripheral neuropathy than in healthy age-matched controls. Therefore, rehabilitation staff must be particularly alert to an increased fall risk in patients with CIPN. Asking cancer patients whether they have fallen recently is a simple screening question for determining heightened fall risk. Impaired gait and balance are the most reliable predictors of this serious medical problem. Results from clinical tests such as the timed up and go, single limb stance, gait analysis, and sensory assessment also provide further assessment of fall risk in CIPN patients.

Therapeutic interventions aimed at reducing fall risk typically include lower extremity strengthening exercises and gait training combined with balance training and issuance of assistive devices. Patient and caregiver education regarding issues such as recognizing potential environmental hazards, performing necessary home and environmental modifications (removing throw rugs, installing adequate lighting, and maximizing visual contrasts), and increasing diligence when the patient is in a novel environment should be provided. For patients with CIPN who also have cognitive, visual, or auditory deficits, caregiver education is of particular importance.

The presence of peripheral neuropathy can also contribute to detrimental changes in gait patterns. In a study of 24 older women, those with peripheral neuropathy showed a gait pattern that was slower and less efficient as measured by various gait parameters (e.g., increased step time) than the control group, with differences magnified under challenging walking environments. Clinical gait assessment involves visual and auditory observation of gait pattern, shoe wear (e.g., marred shoe top may indicate foot drag), foot slap, and toe dragging. Biomechanical analysis systems are available that provide sophisticated quantitative analysis of specific gait parameters. Gait training typically incorporates balance training, lower extremity strengthening, endurance activities, and walking under simple (smooth, level surface) and complex conditions (time constraints, physical load, and terrain obstacles). Labor-intensive programs, such as training with body weight support systems, are more widely used for stroke patients but may be useful for patients with CIPN. Appropriate assistive devices (canes, walkers, and ankle-foot orthoses) can also be helpful for improving gait characteristics.

Identifying muscle weakness caused specifically by CIPN is difficult because this condition can be the result of a variety of factors already present in many cancer patients, including deconditioning, fatigue, nutritional deficiency, sleep disorders, depression, medication regimens, and pre-existing neurologic disorders. Chemotherapeutic agents that cause CIPN damage sensory neurons much more frequently than motor neurons, reducing the likelihood that muscle weakness is associated with CIPN. Of note, many cancer patients receive corticosteroids, a drug well-known for its muscle-wasting effects, particularly on respiratory and proximal lower extremity muscles.

Regardless of the cause of muscle weakness, muscle function must be assessed in these patients. Manual muscle testing of specific muscles or muscle groups is the most frequently used method of assessing muscle strength. Hand-held dynamometers can be used to directly measure specific muscle strength or infer muscle strength such as grip strength. Ul-
Ultrasound is used to image skeletal muscle for architectural changes consistent with decreases in muscle strength. Therapeutic management schemes for increasing muscle strength are similar whether muscle loss is attributable directly to CIPN or indirectly to other cancer-related causes. Resistance training is consistently shown to be effective in improving muscle strength. For example, a 9-hour weekly training program over 6 weeks increased muscular strength by an average of 41% in 70 cancer patients undergoing chemotherapy. One key to a successful exercise program is to distinguish patients who require supervision in an inpatient or outpatient training program from self-motivated patients who often derive comparable or greater benefit from participating in a self-directed exercise program.

Special attention must be paid to safety for cancer patients engaging in exercise and physical training (Table 6). Physicians and rehabilitation therapists should observe contraindications for training to avoid injury and symptom exacerbation. Attention must also be paid to the use of proper footwear, daily foot inspections, and reporting foot injury.

As with muscle weakness, cancer patients with CIPN may have difficulties performing activities of daily living because of sensory and motor loss. Successful rehabilitation of these deficits requires that they first be identified. Then strategies must be developed to either correct or compensate for the deficit and maximize patient independence. Therapeutic interventions may include musculoskeletal therapies (strengthening, range of motion), environmental modification, teaching energy conservation techniques, and providing adaptive equipment. Practical adaptive approaches adopted by occupational therapists are very helpful:

- Modifying tasks, such as switching to loafer-style shoes or using Velcro shoe laces
- Providing adaptive equipment, such as enlarged handles on eating utensils, buttonhooks, Velcro on computer keys to stimulate sensation
- Teaching increased use of vision and attention when performing household tasks
- Increasing proprioceptive input, such as putting weights on the patient’s arm for better proprioception
- Educating patients on protective household adaptation
- Strengthening

### Table 6  Safety Notes and Tips in the Management of Functional Deficits

**Avoid or Discontinue Physical Training If:**
- Resting diastolic blood pressure > 115 mm Hg or resting systolic blood pressure > 200 mm Hg
- Diastolic pressure rises > 10 mm Hg above resting value and systolic pressure > 250 mm Hg
- Heart rate to increase with increasing exertional demand
- Signs of poor perfusion (light-headedness, confusion, pallor, cyanosis, or cold and clammy skin) are present or become present
- Angina or angina-like symptoms are present or begin
- Body temperature > 38°C
- Hemoglobin < 8.0 g/dL
- Ongoing bleeding or fresh petechiae or bruises are present; sample question: “Do you bleed often while brushing your teeth?”

**Footwear**
- Avoid heels
- Insoles should not be too soft
- Grip surface on shoes
- Loafer-style, Velcro straps if having difficulty with shoelaces
- Examine feet for signs of injury including abrasions, blisters, etc.

**Orthosis**
- Watch out for skin abrasion
- Wear protective clothing underneath the orthosis
- Select good shoes with proper support, have a closed back and toe, come up over the top of the feet and have a slightly wider width to accommodate the orthoses
- Remove if pain occurs, see the orthotist if pain persists

**Household Environment**
- Avoid or protect against thermal stress (reduce hot water temperature, wear gloves, use potholders)
- Keep rooms well-lit, use night lights
- Remove or tack down loose rugs
- Tidy loose wires across hallways
- Use non-slip bath mats
- Employ energy conservation

### Recommendations:

The Task Force panel emphasized the importance of physicians integrating the identification and assessment of functional deficits into the evaluation of patients with CIPN. Sample questions and simple skill tests that oncologists can use to accomplish this are listed in Table 3. Overall, panelists strongly recommend referring patients with...
CIPN that interferes with functioning to a physical or occupational therapist. Therapeutic interventions, education, and practical advice provided by these rehabilitation specialists can prove invaluable in helping patients to both correct CIPN-induced functional deficits and to cope with the difficulties and challenges these deficits cause in their everyday life.

**Management of Autonomic Symptoms**

Although CIPN primarily affects sensory nerves, autonomic impairment is sometimes seen after the use of antineoplastic agents such as vincristine, cisplatin, carboplatin, paclitaxel, and bortezomib. For example, in a phase II study of bortezomib in patients with metastatic neuroendocrine tumors, 6 of 10 patients with moderate sensory neuropathy also experienced grade 2 to 3 dizziness, orthostasis, syncope, ileus, or abdominal cramping. As discussed, it is difficult to specifically attribute autonomic symptoms to a single drug because other cancer-related factors may also be involved. Autonomic neuropathy induced by chemotherapy has not been well documented or studied.

**Recommendations:** Autonomic dysfunction can manifest with a wide variety of symptoms. The more common symptoms seen in patients undergoing chemotherapy are dizziness or lightheadedness related to orthostatic hypotension, bloating, urinary retention, constipation or diarrhea, and impotence. The EFNS developed guidelines on the management of orthostatic hypotension. Advice for mild cases include getting up slowly (supine position to sitting, sitting to standing) as well as maintaining adequate salt intake and hydration. Abdominal binders or graded compression stockings decrease venous pooling and may be helpful for some patients. For more severe cases, midodrine, fludrocortisone, or their combinations may be prescribed.

Urinary retention can often be related to underlying medical disorders such as benign prostatic hyperplasia or an obstructive tumor and worsened by treatment with medications that have anticholinergic properties such as TCAs and opioids. In such cases, discontinuation of the offending agent may result in resolution of symptoms. The addition of alpha-blocking medications may be indicated in patients with benign prostatic hyperplasia. Chronic urinary retention from neurogenic bladder can be effectively managed using hygienic, intermittent self-catheterization (reviewed by Selius and Subedi). Low-friction, hydrophilic-coated catheters are preferable over regular catheters for the prevention of urinary tract infection. Use of urethral indwelling catheters is not recommended due to possible complications such as sepsis, stones, prostatitis, urethral erosions, and development of squamous cell carcinoma.

Constipation can also be related to underlying medical disorders, including obstruction by tumor, electrolyte abnormalities, and endocrine dysfunction such as hypothyroidism, and worsened by treatment with medications, particularly opioids. A well thought-out bowel program may include adequate water and fiber intake, stool softeners, and, when needed, cathartic agents. The timing of cathartic agents should be deliberate, with the goal of producing bowel movement at a specific time of day. For instance, the use of agents before sleep coupled with the ingestion of breakfast and warm liquid may help reliably produce a morning bowel movement in some patients. Methylnaltrexone is an effective medication for opioid-induced constipation, but its efficacy is unclear when constipation is related to autonomic neuropathy from chemotherapy.

**Conclusions**

With the continued use of neurotoxic drugs, emergence of newer neuropathy-inducing antineoplastic agents, and the adoption of dose-dense regimens, the problem of CIPN is more relevant than ever in oncology. In reviewing the current literature, panelists noted a paucity of rigorous studies on the assessment, prevention, and management of cancer treatment-related neuropathy. More well-designed, sufficiently powered trials specifically on patients with CIPN are necessary to validate evaluation tools, explore different combinations and sequence of pain medications, and test the efficacy and safety of therapeutic methods and preventative supplements.

In the interim, improving education and awareness within both the medical and general community will be an essential primer in efforts to overcome neuropathy. Physician and patient education are required to address the issues of underdiagnosis, underassessment, and failure of intervention. Patient participation in clinical trials is strongly encouraged.

While the community awaits more study data, existing measures can aid patients with CIPN. A
number of medications are available to mitigate neuropathic pain, as are various interventional measures and devices to improve or compensate for functional deficits. For patients for whom pain medications are ineffective, noninvasive techniques such as TENS or acupuncture may be considered.

References


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