 Advances in supportive care have increased the likelihood that previously less common adverse effects of chemotherapy will be more evident. The incidence of chemotherapy-induced peripheral neuropathy (CIPN) is increasing because more neurotoxic drugs have been developed and because patients are living longer and receiving multiple chemotherapy regimens. This article reviews the anatomy of the peripheral nervous system, the proposed mechanisms of CIPN, and manifestations of CIPN from vinca alkaloids, taxanes, and platinum analogs. Major topics of this article are evidence-based data regarding symptom management, a review of medical management, and a synthesis of nursing care for patients at risk for or experiencing CIPN.

At a Glance

✦ Understanding the peripheral nervous system is important because it is sensitive to the effects of neurotoxic agents.

✦ Vincristine, taxanes, and platinum analogs most commonly cause bilateral sensory neuropathy in a stocking-glove distribution.

✦ Nurses need some understanding regarding medical management, such as altering chemotherapy doses, administering drugs that may decrease neuropathy, and planning and implementing skilled care of patients at risk for or experiencing chemotherapy-induced peripheral neuropathy.

The Peripheral Nervous System

A brief review of PNS structures and functions is useful to understand the pathophysiologic mechanisms of CIPN. The PNS and CNS transmit, integrate, interpret, and respond to information from the external and internal environments. The CNS (brain and spinal cord) is protected by the blood-brain vascular barrier that inhibits diffusion of large molecules, highly charged ions, and many drugs from the bloodstream into CNS tissues (Willis, 2000). A similar vascular barrier does not protect the...
PNS, including the afferent and efferent neurons and the dorsal root ganglia of spinal nerves.

The nerve roots of spinal nerves exit vertebral body foramina to innervate their corresponding dermatomes (see Figure 1). Spinal nerves are highly complex and consist of many bundles of afferent and efferent nerve fibers, arteries and veins, and connective tissue surrounded by a tough epineurium. Each individual peripheral nerve fiber, or neuron, consists of a single axon surrounded by Schwann cells forming the myelin sheath, a cell body, and a variable number of dendrites that synapse with other nerves. Neuronal cell bodies are not contained within their axons. Rather, sensory neuron cell bodies are bundled together in the dorsal root ganglia, whereas motor nerve cell bodies are located in the gray matter of the ventral spinal cord within the blood-brain barrier (see Figure 2). Substances move through an axon to the cell body by fast axonal transport, which requires energy, or by dissolution during slow axonal transport. The ventral (motor) and dorsal (sensory) roots of each spinal nerve join as they exit the spinal cord. Afferent fibers are the axons of the sensory PNS, which range from a few millimeters to greater than a meter long and transmit impulses from the periphery to the CNS (Willis, 2000). Sensory information arises from skin, viscera, and cranial nerves. Exteroceptive fibers transmit impulses for touch, pain, temperature, and vibration from skin, whereas proprioceptive neurons include stretch receptors in muscle, joint, and tendon receptors. Visceral nerves carry sensory messages from the internal organs and blood vessels, and cranial nerves from the visual, auditory, olfactory, and vestibular sense organs. Efferent nerve fibers are the axons of the motor PNS and transmit impulses from the CNS to the ventral spinal cord, then to one or both branches of the motor nervous system—the somatic or autonomic (sympathetic or parasympathetic) (Willis).

When a stimulus exceeds the resting threshold of a sensory or motor neuron, a nerve impulse occurs as sodium and potassium ions move across the cell membrane to alter the flow of electrical charges along the neural cell membranes. Voltage-gated sodium-potassium channels open transiently when nerve membranes are depolarized and regulate the excitability of the cells. The speed of impulse transmission depends on whether a neuron is highly myelinated (fastest transmission), lightly myelinated (slower transmission), or unmyelinated (slowest transmission). Motor neurons and sensory neurons for vibratory sense, proprioception, and light touch have large myelinated axons. Autonomic neurons, sensory neurons for temperature, and many pain neurons have small myelinated axons, whereas some pain and temperature impulses are carried on small, unmyelinated fibers (Poncelet, 1998).

**Pathogenesis of Nerve Damage in Chemotherapy-Induced Peripheral Neuropathy**

Peripheral neuropathies can result from damage to axons, myelin sheaths, or cell bodies (Poncelet, 1998). The pathogenesis of CIPN is not understood completely and may vary depending on agents administered. Chemotherapy drugs are believed to first damage sensory axons, then to cause degeneration and dying
back of axons and myelin sheaths. Similar to neuropathies caused by other toxins or metabolic abnormalities, CIPN is symmetrical and begins in the distal end of the longest axons (i.e., the toes of both feet). Ultimately, toxins are transported proximally along the axon toward the cell body. CIPN usually progresses from toes to feet to ankles and then to lower legs (stocking distribution). CIPN in the upper extremities (glove distribution) typically occurs later and moves from fingertips to fingers to hands and so on. However, some patients notice CIPN in their hands first.

Axons can regenerate if the offending agent is removed, but damage to cell bodies often is not completely reversible (Poncelet, 1998). The mechanisms of neuronal repair are not well understood but may involve circulating nerve growth factor (NGF), which has a role in protecting the dorsal root ganglia (Cavaletti et al., 2002; De Santis et al., 2000). NGF is reduced after neurotoxic chemotherapy (cisplatin, oxaliplatin, and paclitaxel). In some animals, exogenous NGF administration prevents or reverses cisplatin-induced structural changes and CIPN from cisplatin, vincristine, or paclitaxel (Aloe, Manni, Porperzi, De Santis, & Fiore, 2000; Quasthoff & Hartung, 2002).

**Risk Factors**

Risk factors for CIPN include specific chemotherapy agents, total cumulative dose, previous and concomitant administration of other neurotoxic chemotherapy drugs, and perhaps large single doses or rapid infusion. Although the overall incidence of CIPN is not known, it is documented most frequently with vincristine, taxanes, and platinum analogs. Current evidence shows that CIPN is largely underreported because of limitations of toxicity grading scales used in clinical trials (Hausheer, Schilsky, Bain, Berghorn, & Lieberman, 2006). Furthermore, the prevalence of CIPN is likely to increase as patients live longer with cancer and receive multiple neurotoxic chemotherapy agents.

Patient-specific risk factors, particularly preexisting sensory neuropathy, also may increase the risk for CIPN. Peripheral neuropathy can have other etiologies, including alcoholism, nutritional problems, diabetes, HIV and other immunosuppressive illnesses, congenital neuropathy, other neurotoxic medications, and exposure to certain toxins or metals (du Bois et al., 1999; Hughes, 2002; Poncelet, 1998) (see Figure 3). In addition, rare individuals with cancer develop a paraneoplastic neuropathy such as paraneoplastic encephalomyelitis or asymmetric sensory neuropathy or carcinomatous or lymphomatous sensory neuropathy (Poncelet; Storstein & Vedeler, 2005). Older age is assumed to be associated with decreased ability to tolerate chemotherapy and increased likelihood of adverse effects, including CIPN. Little evidence supports or refutes the accuracy of such assumptions. One small study of CIPN after paclitaxel- and cisplatin-based regimens found that the incidence and severity of CIPN were no greater in patients older than 65 than in younger patients (Argyriou et al., 2006).

Neuropathy is less common after radiation therapy or surgery for cancer. Because radiation therapy is a local treatment, posttherapy plexopathies usually are focal and unilateral. Surgery might be a mediating factor for recurrent CIPN in patients who received oxaliplatin before surgery. For instance, in a small sample of patients with advanced colorectal cancer who underwent surgical resection of liver metastases after oxaliplatin, 58% (7 of 12) developed postsurgical exacerbation of CIPN (Gornet et al., 2002). Patients had undetectable oxaliplatin serum levels before surgery but high serum concentrations postoperatively. The proposed potential mechanism of recurrent CIPN was that platinum that had been bound to red blood cells may have been liberated by hemolysis or diffusion during surgery.

**Manifestations of Chemotherapy-Induced Peripheral Neuropathy**

Neuropathy after chemotherapy usually is a sensory peripheral neuropathy, whereas motor CIPN and autonomic CIPN are uncommon. Sensory CIPN can be accompanied by negative or positive symptoms (Wolfe & Trivedi, 2004). Negative manifestations include numbness or reduced sensation; positive symptoms are oddly painful sensations such as paresthesia, dysesthesia, causalgia, and allodynia (see Table 1). Damage to large sensory nerves results in decreased deep tendon reflexes and vibratory sense (in ankles before wrists), ataxia, and abnormal position sense of body parts. Lhermitte’s sign is an unusual symptom of peripheral neuropathy that reflects damage progressing to the level of the spinal cord. It causes an electric, shock-like feeling that shoots down the back and sometimes into limbs with neck flexion.

### Possible Etiologies of Symmetric Peripheral Neuropathies

**Endocrine diseases**
- Diabetes mellitus
- Hypothyroidism

**Nutritional diseases**
- Alcoholism
- Vitamin B12 deficiency
- Thiamine deficiency
- Vitamin E deficiency
- Folate deficiency
- Postgastrectomy syndrome
- Crohn disease

**Connective tissue diseases**
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polyarteritis nodosa
- Sjögren syndrome

**Infectious diseases**
- AIDS
- Lyme disease

**Hereditary diseases**
- Charcot-Marie-Tooth syndrome
- Friedreich’s ataxia
- Other sensory neuropathies

**Metal neuropathy**
- Chronic arsenic intoxication
- Mercury
- Gold
- Thallium

**Toxic neuropathy**
- Acrylamide
- Carbon disulfide
- Dichlorophenoxyacetic acid
- Ethylene oxide
- Carbon monoxide
- Glue sniffing

**Other**
- Amyloidosis
- Sarcoidosis
- Primary biliary cirrhosis
- Uremia
- Vasculitis
- Ischemic lesions

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**Figure 3. Possible Etiologies of Symmetric Peripheral Neuropathies**

*Note. Based on information from Hausheer et al., 2006; Hughes, 2002; Poncelet, 1998.*
Teasing out manifestations of motor neuropathy (e.g., weakness, loss of feeling, foot pain), which may be related to sensory damage, is difficult. Few agents cause autonomic CIPN, but decreased efferent impulses to gastrointestinal or urinary organs can cause nausea, abdominal fullness or bloating, early satiety, constipation, difficult initiating or controlling urinary stream, incomplete bladder emptying and overflow incontinence, and erectile dysfunction. Autonomic neuropathy of cranial nerves may manifest with blurred or double vision, orthostasis, and decreased sweating.

### Chemotherapeutic Agents Associated With Chemotherapy-Induced Peripheral Neuropathy

Vinca alkaloids, taxanes, and platinum analogs are implicated most commonly in dose-limiting CIPN; less commonly, high-dose ifosfamide, high-dose methotrexate, etoposide, procarbazine, cytarabine, suramin, bortezomib, thalidomide, and arsenic trioxide (see Table 2). CIPN may occur during or soon after chemotherapy administration, progress with increasing total doses, or worsen after some drugs have been stopped, which is called coasting (Chaudhry et al., 2002; Frisk, Stalberg, Stromberg, & Jakobson, 2001; Lazo et al., 2003; Quasthoff & Hartung, 2002; Richardson et al., 2003; Verstappen, Heimans, Hoekman, & Postma, 2003). CIPN is persistent and usually partially reversible over weeks to months after chemotherapy completion. Severe CIPN may be irreversible, and patients may have residual numbness and tingling in their hands and feet years after completing chemotherapy (Nail, 2001).

### Vincristine

Vinca alkaloids, especially vincristine, are neurotoxic to the sensory and autonomic PNS. Other vinca alkaloids are less likely to cause CIPN. Vinblastine causes bone marrow suppression before CIPN, whereas vindesine and vinorelbine lead to mild CIPN evidenced by lost deep tendon reflexes (Verstappen et al., 2003). Vincas bind to intracellular microtubules, causing intracellular edema of sensory axons and dose-dependent, stocking-glove CIPN with paresthesias, pain, distal hypesthesia, and lost deep tendon reflexes (Quasthoff & Hartung, 2002). Impaired hepatic function increases the likelihood of CIPN from vincristine, even

<table>
<thead>
<tr>
<th>TERM</th>
<th>SYNONYM</th>
<th>DEFINITION</th>
</tr>
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<tbody>
<tr>
<td>Allodynia</td>
<td>Hyperesthesia, hyperalgia</td>
<td>Excessively, abnormally increased pain sensitivity to nonpainful stimuli</td>
</tr>
<tr>
<td>Ataxia</td>
<td></td>
<td>Loss of coordination, clumsiness; may affect limbs, trunk, speech, and eye movements</td>
</tr>
<tr>
<td>Causalgia</td>
<td></td>
<td>Burning pain, often associated with abnormal autonomic changes in skin (e.g., vasoconstriction or dilatation, abnormal sweating, warmer or colder than surrounding areas, smooth appearance); intensified by warmth or cold</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td></td>
<td>Unpleasant abnormal sensations in the skin that can be spontaneous or evoked with nonpainful tactile stimulation; may feel like painful electric sensations, tingling, prickling, or cutting of the skin</td>
</tr>
<tr>
<td>Glove and stocking syndrome</td>
<td></td>
<td>Because the longest spinal nerves are more vulnerable, manifestations start symmetrically in the toes and fingers.</td>
</tr>
<tr>
<td>Hyperesthesia</td>
<td></td>
<td>Increased sensitivity to sensory stimuli; greater than would be expected; nonpainful, but may be cramping; worse at night</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>Hypesthesia</td>
<td>Impaired (decreased), dulled tactile sensitivity</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td></td>
<td>Decreased deep tendon reflexes; can result from altered sensory or motor neuron conduction</td>
</tr>
<tr>
<td>Hypotonia</td>
<td></td>
<td>Decreased or lessened muscle tone; results from motor (efferent) neuropathy</td>
</tr>
<tr>
<td>Lhermitte’s sign</td>
<td>Barber chair phenomenon</td>
<td>An electric, shock-like sensation induced by flexing the neck; extends down the spine and shoots into the limbs</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td></td>
<td>Can occur with peripheral nerve damage or damage at the level of the nerve root or spinal cord; described as different, burning, shooting, sharp-cutting, or lancinating</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>Loss or lack of sensation, sensory loss</td>
<td>Evoked spontaneous sensations (occur without stimulus); may include feeling of warmth or burning, tingling, cold, pins and needles sensations (prickling), numbness, or feeling like limb has fallen asleep</td>
</tr>
<tr>
<td>Proprioception</td>
<td></td>
<td>Ability to sense body or body part position, location, orientation, and movement</td>
</tr>
</tbody>
</table>

Note: Based on information from Backonja & Serra, 2004; Poncelet, 1998; Visovsky, 2003; Wolfe & Trivedi, 2004.
Table 2. Chemotherapy Agents That Can Cause Peripheral Neurotoxicity

<table>
<thead>
<tr>
<th>CLASS AND DRUG</th>
<th>NEUROTOXIC CUMULATIVE DOSE</th>
<th>PERIPHERAL NERVOUS SYSTEM EFFECTS</th>
<th>MANIFESTATIONS AND COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vinca alkaloids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>&gt; 4 mg</td>
<td>Sensory: always</td>
<td>• Pain and paresthesia of feet and hands, distal hyperesthesia, then loss of deep tendon reflexes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motor: rare</td>
<td>• Autonomic manifestations: orthostatic hypotension, constipation, ileus, urinary bladder dysfunction, erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autonomic: frequent</td>
<td>• Muscle cramps and weakness may occur in advanced peripheral neuropathy.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Children and adults with hereditary neuropathy can experience rapid-onset quadriplegia after administrations; may be partially reversible over months to years or be permanent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Vincristine and vinblastine can affect cranial nerves, leading to vocal cord paralysis, jaw pain, or (rarely) optic neuropathy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Coasting can occur.</td>
</tr>
<tr>
<td>Vinblastine</td>
<td></td>
<td>Sensory: rare</td>
<td></td>
</tr>
<tr>
<td>Vinorelbine</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

| **Taxanes**          |                             |                                  |                                                                                                                                                              |
| Paclitaxel           | > 175–200 mg/m²            | Sensory: always                  | Paclitaxel                                                                                                                                                   |
|                      |                             | Motor: less frequent             | • Acute chemotherapy-induced peripheral neuropathy (CIPN): At doses > 250 mg/m², 50% of patients have paresthesia and dysesthesia 24–72 hours after treatment; most common—proximal weakness, myalgia in knees and shoulders; less common—nocturnal leg cramps or bone pain; symptoms resolve spontaneously in four to seven days |
|                      |                             | Autonomic: frequent              | • Persistent CIPN: > 70% of patients have dose-related distal-extremity numbness, tingling, and burning pain starting in feet with possible spread to legs; can progress to grade 3 (i.e., difficulty walking) |
|                      |                             |                                  | • 47% have paresthesias of fingers and hands.                                                                                                               |
|                      |                             |                                  | • Some patients have decreased vibratory perception; if severe, it is accompanied by loss of position sense and deep tendon reflexes.                   |
|                      |                             |                                  | • Motor damage is predominant; disabling weakness and motor neuropathy occur in some cases.                                                               |
| Nanoparticle albumin |                             |                                  |                                                                                                                                                              |
| Paclitaxel poliglu-   |                             |                                  |                                                                                                                                                              |
| mexit                  |                             |                                  |                                                                                                                                                              |
| **Docetaxel**         | > 600 mg/m²                 | Sensory: frequent                | Docetaxel: 50% develop severe symptoms of sensory CIPN.                                                                                                     |
|                      |                             |                                  | Paclitaxel and docetaxel: waxing and waning of symptoms; coasting                                                                                          |
|                      |                             |                                  |                                                                                                                                                              |
| **Platinum analogs**  |                             |                                  |                                                                                                                                                              |
| Cisplatin             | > 300–400 mg/m²             | Sensory: frequent                | • CIPN is dose-dependent.                                                                                                                                    |
|                      |                             | Motor: absent                    | • Predominantly sensory with diminished vibratory perception, loss of deep tendon reflexes and paresthesia (tingling to pain) in lower extremities         |
|                      |                             | Autonomic: rare                  | • Sensory ataxia, pronounced gait disturbances, and impaired proprioception in advanced CIPN                                                          |
|                      |                             |                                  | • > 75% develop neurosensory high-frequency hearing loss and tinnitus.                                                                                       |
|                      |                             |                                  | • Rare manifestations: motor neuropathy with muscle weakness and cramps, Lhermitte’s sign (central nervous system toxicity)                          |
|                      |                             |                                  | • Coasting is common and can occur two to six months after cisplatin is completed.                                                                         |
| Carboplatin           | > 400 mg/m²                 | Sensory: less often              | • CIPN after high cumulative doses and with combination regimens                                                                                           |
|                      |                             | Motor: absent                    |                                                                                                                                                              |
|                      |                             | Autonomic: NR                    |                                                                                                                                                              |
| Oxaliplatin Acute (< 14 days) | NA | Sensory: NA | Dose-related acute sensory symptoms 30–60 minutes after administration.                                                                                     |
|                      |                             | Motor: NA                        | • Most common: cold-related dysesthesia and paresthesia of hands and feet                                                                             |
|                      |                             | Autonomic: NA                    | • 20% experience cold-related pharyngolaryngeal dysesthesia; patients report it as shortness of breath and difficulty swallowing.                          |
|                      |                             |                                  | • Must differentiate cold-related dysphagia and dyspnea from severe hypersensitivity reactions, which are not cold-related                               |
|                      |                             |                                  | • Painful paresthesia is less common.                                                                                                                       |
|                      |                             |                                  | • Symptoms resolve in a few days to two weeks.                                                                                                            |

(Continued on next page)

Note. Based on information from Cassidy & Misset, 2002; Cersosimo, 2005; Chaudhry et al., 2002; du Bois et al., 1999; Gamelin et al., 2002; Hausheer et al., 2006; Quastoff & Hartung, 2002; Richardson et al., 2003; Taieb et al., 2003; Visovsky, 2003.
at low cumulative doses. Vincristine-treated patients often develop paresthesias and numbness in their hands before their feet, and the severity of CIPN is related to dose intensity and cumulative dose. Early studies showed that patients given 4 mg every three weeks were much more likely than patients receiving lower doses to develop severe CIPN with coasting in the first month after completing therapy (Verstappen et al., 2005).

In more advanced neuropathy, muscle cramps and weakness of extensor muscles in distal limbs may occur. More than 33% of patients have autonomic nervous system dysfunction manifesting as orthostatic hypotension, postural tachycardia, and other symptoms of sympathetic dysfunction.

### Table 2. Chemotherapy Agents That Can Cause Peripheral Neurotoxicity (Continued)

<table>
<thead>
<tr>
<th>CLASS AND DRUG</th>
<th>NEUROTOXIC CUMULATIVE DOSE</th>
<th>PERIPHERAL NERVOUS SYSTEM EFFECTS</th>
<th>MANIFESTATIONS AND COMMENTS</th>
</tr>
</thead>
</table>
| Oxaliplatin    | > 175–200 mg/m²            | Sensory: always Motor: less often Autonomic: NR | • Non–cold-related dysesthesias and paresthesias of distal extremities that worsen with cumulative dose  
  • More likely with higher single doses (≥ 130 mg/m²) than lower (< 90 mg/m²)  
  • Impaired sensation, sensory ataxia, and/or deficits in fine sensory-motor coordination  
  • Cumulative doses > 1,000 mg/m²: small risk for central nervous system toxicity (Lhermitte’s sign, problems initiating urinary stream)  
  • Symptoms reversible six to eight months after chemotherapy stopped: 80% partial, 40% complete  
  • Low risk exists for ototoxicity, and coasting does not occur. |
| Other          |                            | Sensory: frequent Motor: NR Autonomic: NR | • CIPN is the most significant dose-related effect and may occur early when higher daily doses are given (dose range 25–1,600 mg per day).  
  • Predominantly sensory peripheral neuropathy involves small and large fibers. |
| Thalidomide   | NR                         | Sensory, motor, autonomic: NR | • CIPN rate 31%; 12% grade 3 and dose reduction; 4% drug discontinued because of CIPN |
| Bortezomib    | NR                         | Sensory, motor, autonomic: NR | • CIPN rate 31%; 12% grade 3 and dose reduction; 4% drug discontinued because of CIPN |
| Other (less common) |                  |                               |                           |
| Procarbazine  | NR                         | Sensory < 20% Motor: NR Autonomic: NR | • Intrinsic weakness of hands  
  • Orthostatic hypotension |
| Hemamethylmelamine | NR                       | Sensory and motor reported       | • Tingling, pain, or numbness in the hands or feet |
| Arsenic trioxide | NR                       | Sensory, motor, autonomic: NR | • CIPN may not become evident until the drug is discontinued.  
  • Severe reactions include quadriplegia  
  • Resolution of CIPN may take months. |
| Methotrexate  | NR                         | Sensory: rare Motor: NR Autonomic: NR | • Lumbar radiculopathy  
  • Occasional brachial plexopathy and lateral rectus muscle palsy |
| Suramin (investigational) | Maximal plasma level > 150 mg | Sensory: frequent Motor: less often Autonomic: NR | • Dose-limiting CIPN reported in unmyelinated sensory and motor nerves.  
  • Higher serum levels: 40% develop sensorimotor neuropathy similar to flaccid paralysis; plasma levels must be monitored during therapy.  
  • Motor symptoms: severe paresis, similar to Guillain-Barré syndrome  
  • Neuropathy tends to remit. |
| Other (uncommon or rare) |                  |                               |                           |
| Ifosfamide    | NR                         | Sensory: rare | • Painful axonal peripheral neuropathy  
  • Motor and autonomic peripheral neuropathy have not been reported. |
| Ara-C         | NR                         | Sensory and motor reported       | • Greater risk with high-dose or in combination with daunorubicin and asparaginase |
| Etoposide     | NR                         | Sensory: rare | • Motor and autonomic peripheral neuropathy have not been reported. |

NA—not available; NR—not reported

Note. Based on information from Cassidy & Misset, 2002; Cersosimo, 2005; Chaudhry et al., 2002; du Bois et al., 1999; Gamelin et al., 2002; Hausheer et al., 2006; Quastoff & Hartung, 2002; Richardson et al., 2003; Taieb et al., 2003; Visovsky, 2003.
fested as orthostatic hypotension, constipation (may progress to ileus and megacolon), urinary bladder dysfunction, erectile dysfunction, and altered heart rate (Quasthoff & Hartung, 2002). Few patients develop neuropathy in a single nerve (e.g., femoral neuropathy) or cranial nerve palsies (e.g., vocal cord paresis, diplopia, facial nerve palsy, ophthalmoplegia, sensorineural hearing loss) (Verstappen et al., 2003; Visovsky, 2003). Symptoms may reverse in months to years, worsen after vincristine is stopped, or be irreversible.

**Taxanes**

Taxanes are neurotoxic to Schwann cells and cause “leaky” axonal membranes that lead to nonspecific ion influx into neurons, acute membrane depolarization, altered cytoplasmic flow, and loss of sensory and motor axons (Quasthoff & Hartung, 2002). In addition, the solvent for paclitaxel, polyoxethylene-glycerol (Cremophor® EL, BASF), is believed to be neurotoxic. However, CIPN occurs after administration of taxanes not formulated with Cremophor, including docetaxel, nanoparticle albumin-formulated paclitaxel (Abraxane®, Abraxis BioSciences, Inc.), paclitaxel poliglumex (Xyotax™, AstraZeneca Oncology), and liposomal paclitaxel (Hausheer et al., 2006). Docetaxel may cause mild to moderate, predominantly sensory CIPN with paresthesias, loss of deep tendon reflexes, and altered vibratory sense (Verstappen et al., 2003). Some docetaxel-treated patients experience Lhermitte’s sign and proximal motor weakness.

Dose-limiting CIPN is more common with paclitaxel than with docetaxel. Paclitaxel affects all sensory nerves, especially large myelinated fibers of vibratory sense and proprioception. More than 50% of patients who receive paclitaxel greater than 250 mg/m² have paresthesia and dysesthesia 24–72 hours after treatment (Verstappen et al., 2003). Toxicity to fast-conducting motor neurons causing acute, painful, pathologic, spontaneous muscle activity in the lower legs starts one to two days after paclitaxel infusion. Symptoms resolve in four to seven days without treatment or may be relieved earlier with amitriptyline or an antihistamine (e.g., diphenhydramine, cimetidine, ranitidine) (Verstappen et al., 2003).

CIPN may occur after a single high dose of paclitaxel, particularly if it is administered with cisplatin. CIPN also is related to rapid infusions (less than 24 hours) and total cumulative dose of paclitaxel. Cumulative CIPN is first manifested by paresthesias, numbness, and sometimes pain in the feet and hands. Progressive CIPN can lead to difficulties with writing and buttoning and unsteadiness when ambulating (especially in the dark). Other, later effects include loss of deep tendon reflexes and muscle weakness, as well as potentially disabling motor neuropathy in severe cases (Verstappen et al., 2003). Predicting neuropathy progression, which may progress, lessen, or worsen (coasting) after a taxane is discontinued, is difficult.

**Platinum Analogs**

Platinum analogs have little ability to cross the blood-brain barrier of the CNS but have high affinity for the sensory PNS. Cisplatin, carboplatin, and oxaliplatin accumulate in sensory axons (but not motor neurons) and dorsal root ganglia of afferent sensory axons—both in small, thinly myelinated axons involved in pain and temperature perception and in large sensory fibers involved in proprioception (Hausheer et al., 2006; Verstappen et al., 2003). Accumulating platinum leads to shrinkage of nuclear and cytoplasmic components, disturbed cellular metabolism and axonal transport, and axonal loss in sensory nerves, as well as dorsal root atrophy.

**Cisplatin and carboplatin:** Cisplatin and carboplatin act as calcium channel blockers and disrupt calcium homeostasis in sensory axons, which ultimately results in dorsal root ganglia apoptosis (Gamelin, Gamelin, Bossi, & Quasthoff, 2002). CIPN begins about one month after cisplatin or carboplatin is started; severity is related to cumulative doses and high single doses. CIPN often is dose limiting after cisplatin, but carboplatin is reported to be less neurotoxic, possibly because dosing frequency is limited by hematologic toxicity (Cassidy & Misser, 2002; Gamelin et al., 2002; Verstappen et al., 2003).

The minimum cumulative dose of cisplatin that causes symptoms of CIPN is 200 mg/m², and greater than 400 mg/m² is always neurotoxic (Quasthoff & Hartung, 2002). Cisplatin predominantly affects large myelinated sensory fibers, causing diminished vibratory sense, loss of deep tendon reflexes (distal to proximal), and paresthesias (slight tingling that may progress to pain) (Authier, Gillet, Fialip, Eschalier, & Couadore, 2003). CIPN is severe when it progresses to proprioceptive nerves and then is accompanied by ataxia, muscle cramps, and possibly Lhermitte’s sign. CIPN from cisplatin is difficult to grade because it can begin after the drug has been stopped (coasting), which may be related to persistent drug accumulation in the dorsal root ganglia.

**Oxaliplatin:** Oxaliplatin directly affects neurons and interferes with ion conductance in axons, which induces acute hyperexcitability of motor and sensory neurons. Oxaliplatin, which has little to no cross-resistance to other platinum analogs, causes two distinct types of CIPN: acute, self-limiting CIPN and delayed, cumulative sensory CIPN. About 90% of patients experience acute CIPN that starts during or within one hour after oxaliplatin administration, completely resolves in days to weeks, and recurs with subsequent oxaliplatin doses (Hausheer et al., 2006; Quasthoff & Hartung, 2002). Acute CIPN is believed to occur because oxalate, an oxaliplatin metabolite, chelates intracellular calcium and magnesium and impairs voltage-gated sodium channels (Gamelin et al., 2004; Grolleau et al., 2001).

The most common symptoms of acute oxaliplatin-related CIPN are dysesthesia and paresthesias induced or exacerbated by exposure to cold (e.g., drinking cold beverages, eating cold foods, touching cold surfaces, putting a hand in cold water, suddenly being exposed to air conditioning) (Cassidy & Misser, 2002). Some patients have painful jaw contractions or a distressing sense of being unable to swallow or breathe (Wilkes, 2005). Patients may describe symptoms in their hands and feet as “muscle cramps,” “spasms,” “stiffness,” or “tightness” and may be unable to release their handgrips. If such sensations occur in the feet, they may progress to the legs. Acute CIPN can be frightening and uncomfortable but usually is not dose limiting. Acute symptoms are related to dose and administration rate, and they peak within 24–48 hours (Verstappen et al., 2003). Patients who receive higher doses (130 mg/m² versus 85 mg/m²) over shorter times (one hour versus six hours) are more likely to have circumoral, oral, and pharyngeal dysesthesias and/or paresthesias, followed by paresthesias of the hands and feet.
plus throat or eye pain (Gamelin et al., 2002; Lehky, Leonard, Wilson, Grem, & Floeter, 2004).

As many as 19% of patients experience some type of oxaliplatin-related hypersensitivity reaction that must be distinguished from acute CIPN. Frank anaphylaxis is extremely rare; severe hypersensitivity reactions, which are more likely in patients who previously received cisplatin or carboplatin, usually result in discontinuation of oxaliplatin (Sorich, Taubes, Wagner, & Hochster, 2004). Common manifestations of hypersensitivity include erythematous macular rash, facial flushing, palmar erythema, urticaria, and generalized pruritis, which usually resolve with oral antihistamine or dexamethasone and are easily distinguished from acute CIPN. However, hypersensitivity reactions may induce fever, wheezing, dyspnea, and chest tightness or ocular symptoms such as tearing or blurred vision, which may be confused with acute CIPN (Lenz, Hacker, Kern, Schalhorn, & Hiddemann, 2003).

Cumulative oxaliplatin-induced CIPN is accompanied by distal-extremity dysesthesia and paresthesia that persist between cycles and worsen with cumulative doses. For instance, 10%–15% of patients who receive total doses of 780–850 mg/m² of oxaliplatin and 50% of those who receive 1,170 mg/m² develop grade 3 cumulative CIPN (Grothey, 2003). Cumulative CIPN may be accompanied by impaired sensation, sensory ataxia, and deficits in fine sensory motor coordination (Gamelin et al., 2002). In addition, a small proportion of patients who receive greater than 1,000 mg/m² develop Hermitte’s sign or urinary retention (Cassidy & Misset, 2002; Taieb, Trillet-Lenoir, Rambaud, Descos, & Freyer, 2002).

## Grading the Severity of Chemotherapy-Induced Peripheral Neuropathy

Several scales grade the severity of CIPN, including one that is specific for oxaliplatin (Postma & Heimans, 2000; Winegarden et al., 2004). Some of them are included in Table 3. Grade 2 or greater CIPN is assumed to be associated with negative QOL effects (Quasthoff & Hartung, 2002). However, commonly used toxicity scales have limitations in that they provide only global measures, are ambiguous and unidimensional, are not evidence based, and are not sufficiently sensitive or specific to detect early manifestations of CIPN, including pain (Polomano & Bennett, 2001; Visovsky, 2005).

The most important objective in evaluating CIPN is to determine resultant levels of functional impairment that patients experience in activities of daily living (ADLs) to guide decision making about continuing chemotherapy, reducing doses, or withdrawing neurotoxic drugs (Hausheer et al., 2006). Currently used toxicity criteria are open to wide interpretation, which is related to significant under-recognition and underreporting of CIPN. For instance, in one study of 37 patients receiving neurotoxic chemotherapy, two neurologists independently rated the severity of CIPN using four commonly used criteria (Postma et al., 1998). The inter-rater agreement between the neurologists varied across all scales, as did their ratings of CIPN severity. The issues are at least as likely to affect severity ratings when non-neurology specialists use the scales.

More recent research has focused on evaluating patients’ perspectives with patient-reported tools. One study of patients with ovarian cancer who were treated with cisplatin-based chemotherapy evaluated the reliability and validity of a subjectively rated scale for peripheral neuropathy and functional status. Patient ratings of peripheral neuropathy symptoms and rating score changes correlated with the medical study group neurotoxicity scale used in the study. The authors concluded that the patient-scored CIPN scale was psychometrically sound and clinically efficacious and ideally should lead to a clinically useful tool (Almadrones, McGuire, Walczak, Florio, & Tian, 2004).

In another study, patients receiving oxaliplatin and capecitabine (every three weeks) for colorectal cancer kept detailed diaries that characterized the incidence (yes or no), severity (minimal to very prominent), and effects on ADLs (hardly at all to extremely bothered) of upper-extremity, lower-extremity, and orofacial peripheral neuropathy (Leonard et al., 2005). Oxaliplatin doses were reduced or discontinued based on strict medical criteria for CIPN. The majority of patients in the sample experienced (medically rated) grade 1 dyesthesia and paresthesia, but some patients also reported functional impairment that affected ADLs. Patients’ duration of CIPN increased with cumulative oxaliplatin doses; the median duration of dyesthesias was 5 days after cycle 1 but 21 days after 12 cycles, and paresthesias persisted for a median of 7 days and 21 days, respectively. The most common acute orofacial manifestation was painful cold sensitivity (> 80%), followed by pain with initial bite of food (60%) and pharyngolaryngeal dysesthesia (almost 40%), which often was perceived as a distressing awareness of their breathing that required treatment with an anxiolytic. Other acute CIPN symptoms that occurred in less than 20% of patients included ptosis, sensation of heaviness in the legs, hoarseness or voice changes, visual field deficits, and ocular pain (Leonard et al.).

Boehmke and Dickerson (2005) undertook a phenomenologic study to describe the lived experience of women undergoing dose-intense adjuvant chemotherapy (four cycles of doxorubicin and cyclophosphamide followed by four cycles of paclitaxel) for breast cancer, specifically the meaning of symptoms and symptom experiences as they relate to symptom distress. For the women, numbness in the operative site was a greater concern than pain after surgery, and severe bone pain and peripheral neuropathy were the most distressing symptoms after paclitaxel. Women often described the symptoms in relation to how they affected daily life, such as their return to work being impeded by burning in feet that was exacerbated by standing, feet feeling so numb that the patients could no longer walk, not being able to play the piano because of numbness in the fingers, and numbness affecting manual dexterity (one patient reported a frustrating inability to button clothes or close doors). This type of information certainly is not captured in currently used CIPN scales.

Hausheer et al. (2006) also have tried to capture clinical features of acute and persistent CIPN in two scales: the Patient Neurotoxicity Questionnaire (PNQtaxane/cisplatin/carboplatin) and a modified version for oxaliplatin (PNQoxaliplatin). The self-administered patient questionnaires were designed to identify clinically significant functional impairment from CIPN and to overcome the issues of high variability among raters and the
underreporting of CIPN. The PNQtaxane/cisplatin/carboplatin and PNQoxaliplatin are being used in current studies of an investigational neuroprotective agent for prevention of CIPN (Hausheer et al.).

Medical Management of Chemotherapy-Induced Peripheral Neuropathy

As mentioned, accurate assessment of CIPN is important to decisions regarding continuing planned doses, decreasing doses, or stopping neurotoxic agents. CIPN might be considered undesirable but tolerable when the goal of chemotherapy is cure; however, the same degree of CIPN may not be acceptable for patients receiving palliative chemotherapy. Grade 3 cumulative CIPN always is considered dose-limiting (Quasthoff & Hartung, 2002), but this is a problematic issue because neurotoxic drugs may actually enhance QOL by extending disease-free intervals and alleviating distressing symptoms. Therefore, pharmacologic and nonpharmacologic measures to reduce symptom severity and distress from CIPN are extremely important.

Two common strategies to minimize risk for CIPN are longer administration times to decrease peak serum levels and a planned stop-and-go treatment approach. For instance, common oxaliplatin schedules are smaller doses two or three times a week instead of a single, larger weekly dose; a six-hour instead of one-hour infusion; or a continuous infusion over 86–120 hours (Cassidy & Misset, 2002; Grothey, 2003). With the stop-and-go strategy, the neurotoxic agent is stopped at a predetermined dose or when the patient progresses to grade 3 CIPN, and the agent may be resumed at lower doses when symptoms lessen or at tumor progression (Gamelin et al., 2004). For instance, vincristine would be discontinued (or held until symptoms decrease) if a patient receiving it developed muscle weakness (Verstappen et al., 2003).

Evaluating the efficacy of stopping and later reintroducing oxaliplatin is the focus of ongoing OPTIPMOX trials. In OPTIMOX1, 620 patients with advanced colorectal cancer were randomized to one of two arms. Patients in arm A received FOLFOX4 (oxaliplatin 85 mg/m² plus leucovorin [LV] and fluorouracil [5-FU]) every two weeks until progression of unacceptable toxicity, and those in arm B received FOLFOX7 (six cycles of oxaliplatin 130 mg/m² plus LV and 5-FU) every two weeks followed by 12 cycles of LV plus 5-FU and then reintroduction of FOLFOX7 for six cycles (Tournigand et al., 2006). Patients in arm A received a median of 11 cycles of FOLFOX4, whereas those in arm B received a median of six cycles of FOLFOX7. No differences were found in objective tumor response criteria and median survival (> 20 months) in either group. Only 40.1% who received FOLFOX7 were able to receive oxaliplatin at the second interval. Eleven percent of patients could not receive the oxaliplatin because of residual CIPN higher than grade 1, whereas 17.5% cited no specific reason. Research focusing on stop-and-go oxaliplatin is being pursued in the current OPTIMOX2 trial (Tournigand et al.).

Table 3. Grading Scales for Chemotherapy-Related Peripheral Neuropathy

<table>
<thead>
<tr>
<th>SCALE</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI-CTCAE Motor</td>
<td>Asymptomatic; detected on examination or testing only</td>
<td>Symptomatic weakness interfering with function but not interfering with ADLs</td>
<td>Weakness interfering with ADLs; bracing or assistance to walk (e.g., cane, walker) indicated</td>
<td>Life threatening; disabling (e.g., paralysis)</td>
</tr>
<tr>
<td>Sensory</td>
<td>Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function</td>
<td>Sensory alteration or paresthesia (including tingling) that interferes with function but not with ADLs</td>
<td>Sensory alteration or paresthesia interfering with ADLs</td>
<td>Disabling</td>
</tr>
<tr>
<td>ECOG-CTC Motor</td>
<td>Subjective weakness; no objective findings</td>
<td>Mild objective weakness without significant impairment of function</td>
<td>Objective weakness with impairment of function</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Sensory</td>
<td>Mild paresthesias; loss of deep tendon reflexes</td>
<td>Mild or moderate objective sensory loss; moderate paresthesias</td>
<td>Severe objective sensory loss or paresthesias that interfere with function</td>
<td>–</td>
</tr>
<tr>
<td>Oxaliplatin-Specific Scale</td>
<td>Paresthesias or dysesthesias of short duration that resolve and do not interfere with function</td>
<td>Paresthesias or dysesthesias interfering with function but not ADLs</td>
<td>Paresthesias or dysesthesias with pain or with functional impairment that also interfere with ADLs</td>
<td>Persistent paresthesias or dysesthesias that are disabling or life threatening</td>
</tr>
</tbody>
</table>

ADLs—activities of daily living; ECOG-CTC—Eastern Cooperative Oncology Group Common Toxicity Criteria; NCI-CTCAE—National Cancer Institute Common Terminology Criteria for Adverse Effects

Note. Based on information from Eastern Cooperative Oncology Group, n.d.; National Cancer Institute, 2006; Winegarden et al., 2004.
Pharmacologic Interventions for Chemotherapy-Induced Peripheral Neuropathy

Researchers have great interest in identifying agents that might decrease, prevent, or alleviate distressing manifestations of CIPN and negative effects on ADLs, particularly with oxaliplatin. Most of the currently used agents have been derived by logical empiricism, with evidence drawn from the laboratory (i.e., applying neurotoxic chemotherapeutic agents to insect or animal nerve tissues) or from animal studies (Grolleau et al., 2001). Animal and laboratory data may not be transferable to human beings, particularly because study drug concentrations are much higher than ever experienced in patients receiving chemotherapy. In addition, although a few studies have examined pharmacologic interventions for patients experiencing CIPN, most human evidence is extrapolated from anecdotal reports and studies of patients with neuropathies from other causes, such as postherpetic neuralgia, diabetic neuropathy, and trigeminal neuralgia. Agents with neuroprotective potential include calcium/magnesium (Ca++/Mg++), glutathione, vitamin E, and other agents, as well as NGFs (Ocean & Vahdat, 2004).

The rationale for administering IV or oral Ca++/Mg++ as a possible protector against oxaliplatin-induced CIPN is that oxalate, an oxaliplatin metabolite, directly affects calcium chelation and indirectly modifies voltage-gated sodium-potassium channels (Grolleau et al., 2001). Acute CIPN is believed to occur because a temporary dysfunction of the ion channels in nerve cell membranes (a channelopathy) allows platinum influx and increases the excitability of sensory neurons, whereas chronic and progressive CIPN is related to accumulation of platinum in the dorsal root ganglia (Leonard et al., 2005; Saif, 2004). One retrospective case review series concluded that patients who received IV Ca++/Mg++ (1 g each) before and after oxaliplatin were significantly less likely to experience acute CIPN or moderate to severe cumulative CIPN or to withdraw from oxaliplatin chemotherapy than patients who did not receive Ca++/Mg++ (Gamelin et al., 2004). Similarly, a prospective open-label study evaluated Ca++/Mg++ given before and after oxaliplatin (85 mg/m² every two weeks to 130 mg/m² every three weeks) (Gamelin et al., 2002). The 101 patients who received Ca++/Mg++ had a larger cumulative oxaliplatin dose than the 38 patients who did not receive Ca++/Mg++ (910 mg/m² versus 650 mg/m²), were less likely to develop symptoms of acute CIPN (1.6% versus 26%) or any grade of cumulative CIPN (27% versus 75%), and were less likely to withdraw from the study (23% versus 40%).

One interesting case report documented a patient who serendipitously started taking Rolaids® (McNeil-PPC, Inc.), which was assumed to be an oral calcium supplement (they also contain magnesium), and oral magnesium was added to his regimen. The patient was able to complete six additional months of oxaliplatin and was treated to a cumulative dose of 2,500 mg/m². The impact of IV and oral Ca++/Mg++ merits more study (Ocean & Vahdat, 2004).

A great deal of data regarding glutathione has been developed by European investigators (Hausheer et al., 2006). The underlying hypothesis for using glutathione is that it may inhibit cisplatin or oxaliplatin accumulation in dorsal root ganglia. One randomized, double-blind, placebo-controlled Italian study found that IV glutathione before oxaliplatin was superior to placebo to reduce the incidence (43% versus 79%) and severity of CIPN (grade 2–4 neurotoxicity = 10% versus 58%) (Cascinu et al., 2002). No glutathione-treated patient had grade 3 or greater CIPN, and tumor response rates were similar in both groups. The study was limited by its small sample size; although 52 patients were included initially, only 24 were evaluable after eight cycles of oxaliplatin (Cascinu et al.). Glutathione is not available in the United States and many other countries, which also limits clinical trial evaluation of the agent.

The rationale for supplemental vitamin E is that a deficiency of the vitamin causes a sensory peripheral neuropathy with manifestations similar to CIPN. In one open-label pilot study, 31 patients receiving cisplatin, paclitaxel, or both were randomized to supplemental vitamin E (600 mg per day during chemotherapy and as long as three months afterward) or placebo (Argyriou et al., 2005). The same neurologist evaluated all patients at baseline, after the third and sixth cycles, and as long as three months later. Four patients (25%) in the vitamin E group experienced mild or moderate CIPN, whereas 11 patients (73.3%) in the control group developed mild, moderate, or severe CIPN as confirmed by clinical examinations and electrophysiologic studies (Argyriou et al., 2005). Supplemental vitamin E may warrant further study in larger, controlled trials.

The evidence supporting the use of amifostine, glutamate, and glutamine to ameliorate CIPN is inconsistent (Hausheer et al., 2006; Visovsky, 2003). For instance, in one laboratory study, amifostine was neuroprotective to animal cells exposed to paclitaxel and partially reversed cisplatin-related neurotoxicity but had no effect on vincristine-related neurotoxicity (Verstappen et al., 2003). Human studies also have inconsistent results (Moore et al., 2003; Ocean & Vahdat, 2004; Openshaw et al., 2004), and amifostine is emetogenic and costly. Information regarding several ongoing and proposed clinical trials of various agents for prevention or treatment of CIPN (e.g., alpha lipoic acid, glutamine, amifostine, lamotrigine, epoetin alpha, BNP7787) can be found at www.clinicaltrials.gov with the search words “peripheral + neuropathy.”

Another agent of interest is xaliproden, an oral neurotrophic and neuroprotective drug that increased in vitro survival and differentiation of neurons (Susman, 2006). A promising study of the agent was reported at the American Society of Clinical Oncology’s 2006 Gastrointestinal Cancer Symposium (Cassidy et al., 2006). In a randomized, double-blind study, 325 patients received oral xaliproden and 324 patients received placebo for 14 days starting on the day of oxaliplatin-based chemotherapy administration and repeated for a median of 12 cycles. The incidence of grade 3–4 peripheral neuropathy was 39% less in patients who received xaliproden than in those who received placebo (p = 0.02), and tumor response did not vary between the groups (Cassidy et al.). Research in the area of NGF analogs to alleviate CIPN is likely to continue.

Painful Chemotherapy-Induced Peripheral Neuropathy

Other agents used to decrease dysesthetic pain and allostynia that may accompany CIPN include anticonvulsants, tricycl
antidepressants, opioids, and topical agents, which incorporate knowledge about the pathogenesis of painful neuropathy. No data support prophylactic use of any of the medications. Nerve injury to nociceptors (unmyelinated or lightly myelinated sensory fibers) may lead to release of inflammatory mediators that, in turn, cause altered expression of sodium channels in the axon and dorsal root ganglia and possible expression of other ion channels (e.g., calcium, adrenergic) (Beydoun & Backonja, 2005). The result is peripheral sensitization accompanied by altered local electrical properties of the axonal membrane, lowered depolarization thresholds, and ectopic discharges in the nociceptor. Therefore, drugs that have sodium-modulating properties such as anticonvulsants, antidepressants, and local anesthetics may be beneficial for neuropathic pain. Such agents are considered to be adjuvant analgesics and are effective for neuropathic pain from many causes, such as diabetic neuropathy, postherpetic neuralgia, and trigeminal neuralgia, and they may be effective for painful paresthesia, dyesthesia, or allodynia accompanying CIPN (Backonja & Serra, 2004; Gamelin et al., 2002; Wolfe & Trivedi, 2004). Specific questions about which drugs (antidepressants or anticonvulsants) are best for CIPN, when to start, and how to escalate doses are largely unanswered. Other drugs, such as clonidine, corticosteroids, or topical agents, are used occasionally for neuropathic pain (Armstrong, Almadrones, & Gilbert, 2005).

Anticonvulsants may block glutamate, excitatory neuropeptides, and presynaptic calcium channels to ultimately inhibit CNS pain sensitization. Gabapentin is used most commonly for CIPN (Cianfrocca et al., 2006). According to consensus recommendations, gabapentin should be started as a single 100–300 mg dose at bedtime (or 100–300 mg three times a day) and titrated by 100–300 mg daily every one to seven days as needed (Argoff, Katz, & Backonja, 2004). The one-time-per-day dosing schedule simplifies drug taking and may increase adherence. An older anticonvulsant, carbamazepine (Tegretol®, Novartis), has been used for neuropathic pain but can induce aplastic anemia and agranulocytosis. Furthermore, one study that evaluated intermittent carbamazepine (200 mg three times a day for eight days, starting five days before chemotherapy) in 12 patients found that it did not prevent acute CIPN with oxaliplatin, but 7 patients (58.3%) had adverse effects from carbamazepine (Wilson et al., 2002).

A new analog, oxycarbazepine, may alleviate pain refractory to carbamazepine and gabapentin, has few drug interactions, and does not induce agranulocytosis or aplastic anemia (Beydoun & Backonja, 2003). However, it is more expensive and not well studied for neuropathic pain (Criscuolo, Auletta, Lippi, Brogi, & Brogi, 2004). Case-report information indicates that another anticonvulsant, topiramate, may be effective in reducing disabling painful CIPN from oxaliplatin (Durand, Alexandre, Guellevin, & Goldwasser, 2005). More information is needed regarding the safety and efficacy of topiramate.

Tricyclic antidepressants (TCAs), including amitriptyline, desipramine, and imipramine, are used commonly for neuropathic pain (including CIPN), and others also are useful (Verstappen et al., 2003). On the other hand, selective serotonin reuptake inhibitor antidepressants such as fluoxetine are not effective for pain (Paice, 2005). TCAs modulate voltage-gated sodium channels and inhibit reuptake of norepinephrine and serotonin in efferent spinal pathways to decrease pain (Backonja & Serra, 2004; Wolfe & Trivedi, 2004). The adverse effects of TCAs must be monitored. For instance, amitriptyline is more likely than the other TCAs listed to cause anticholinergic effects, cardiac effects, and sedation (Argoff et al., 2004; Cianfrocca et al., 2006). TCAs may be contraindicated for patients with significant cardiac disease, so some clinicians empirically start with an anticonvulsant. Venlafaxine (Effexor XR®, Wyeth Pharmaceuticals Inc.), a newer agent, also has been shown to effectively relieve pain and disability from paclitaxel and oxaliplatin (Durand et al., 2005). TCAs are started at low doses and are dose escalated every three to seven days to an effective dose or to dose-limiting side effects.

Opioids also may be useful for painful PN; doses usually can be increased to an effective range for neuropathic pain from cancer, postherpetic neuralgia, and diabetic neuralgia (Fine, Miaskowski & Paice, 2004; Paice, 2003). Opioid receptors are involved in ion gating, and receptor binding results in the closing of voltage-gated calcium channels of sensory axons (Beydoun & Backonja, 2005). A long-acting formulated opioid (e.g., morphine, methadone) may be preferable, and adding a TCA or anticonvulsant may be opioid dose sparing (Cianfrocca et al., 2006).

Another class of drugs that may have benefit for neuropathic pain is the cannabinoids. Cannabinoid binding at cannabinoid 1 receptors in the CNS is known to modulate neuropathic pain (Hohmann, 2005). Researchers have a great deal of interest in the endocannabinoid system, and many studies of cannabinoids for painful CIPN are being conducted in animal models.

Topical analgesic agents such as capsaicin, aspirin, and lidocaine cream might be helpful for painful CIPN (Argoff et al., 2004). Results with capsaicin, the only agent well studied for painful neuropathy, have been mixed and may range from significant pain reduction and improved ability to perform ADLs to worsening pain and intolerable burning after application. Patient teaching includes wearing gloves during application (to prevent burning the hands) and applying the capsaicin cream three or four times a day (Marrs & Newton, 2003).

Nursing Care of Patients With or at Risk for Chemotherapy-Induced Peripheral Neuropathy

Nurses play a critical role in caring for patients at risk for CIPN, including baseline and ongoing assessment during and after treatment, patient teaching, safe chemotherapy administration, symptom management, and timely consultation of other interdisciplinary team members (Sweeney, 2002). A great deal of practical clinical knowledge has been gained with oxaliplatin, but it generally is applicable to patients receiving other neurotoxic agents (see Table 4).

Comprehensive neurologic assessment is clinically impractical and outside many nurses' scope of practice. However, nurses can identify patients who are at risk for CIPN (Polomano & Farrar, 2006) and perform initial and subsequent brief PNS assessment before each chemotherapy cycle. This is relatively easy because CIPN is bilateral, it progresses in a stocking-glove distribution, and sensory symptoms are most common (Poncelet, 1998).
Table 4. Nursing Care of Patients at Risk for or Experiencing Chemotherapy-Induced Peripheral Neuropathy

<table>
<thead>
<tr>
<th>FOCUS OF CARE</th>
<th>RATIONALE</th>
<th>ACTIONS</th>
</tr>
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</table>
| Baseline assessment                  | Identify patients at risk for chemotherapy-induced peripheral neuropathy (CIPN) or with preexistent neuropathy. Sensory nerves are affected most often; bilateral distribution occurs with initial onset at the distal end of the longest neurons (i.e., toes and fingertips). Focused physical assessment: brief neurologic panel with attention to the extremities that patients report as most troublesome | • Assess risk factors: diabetes, chronic alcohol use, arthritis or other connective tissue disease, exposure to heavy metals or industrial toxins, or peripheral vascular disease.  
• Review medications.  
• Assess previous chemotherapy regimens for neurotoxic agents.  
• Ask about current symptoms consistent with peripheral neuropathy (e.g., tingling, numbness, bilateral versus focal); determine whether symptoms are more noticeable in feet or hands.  
• Vibration sense (tuning fork): Start with great toes; if abnormal, move on to ankles and assess wrists (reflects damage to large sensory neurons).  
• Proprioception (locating where a body part is in space): Grasp sides of the great toe and hold away from other toes; show the patient how you move the toe up and down while explaining position. Instruct the patient to close eyes and move the toe up and down while asking him or her to tell you where the toe is. Do with the other great toe and fingers.  
• Deep tendon reflexes (ankles and wrists)  
• Two-point discrimination on forearm: Open a paper clip or safety pin; place one or two points alternating with dull surface on patient’s forearm about 0.5 mm apart to determine whether patient can discriminate one point from two and painful from nonpainful stimuli with eyes closed.  
• Walking-the-line test: Instruct the patient to walk in a straight line from heel to toes (tandem walking); assess for ataxia (inability to walk heel to toe without losing balance or staggering) because of altered proprioception (or cerebellar disease).  
• Stereognosis: Instruct the patient to close the eyes and place a familiar object (e.g., coin, key, paper clip) on his or her palm; ask the patient to tell you what it is. Stereognostic ability depends on touch and position senses. |
| Ongoing assessment, before each cycle | Early recognition, accurate documentation, and reporting of onset and progression of CIPN to accurately grade severity and effects on activities of daily living Ask about signs and symptoms of acute CIPN.                                                                                                                                  | • Manifestations occur during or within one week of treatment.  
• Manifestations resolve less than two weeks after chemotherapy administration.  
• Oxaliplatin: cold-induced symptoms, momentary painful spasms in jaw, hands, or feet; discomfort in the back of the throat  
• Paclitaxel: onset of numbness or tingling; weakness; pain or aching in knees and legs, elbows or shoulders; stumbling or staggering in the first several days after chemotherapy  
• Distinguish from a hypersensitivity reaction, which can occur with oxaliplatin, cisplatin, carboplatin, paclitaxel, docetaxel, and, rarely, ifosfamide, etoposide, and high-dose methotrexate. |
| Patient teaching                      | Self-care measures may enhance safety, comfort, and quality of life.                                                                                     | Oxaliplatin, acute CIPN  
• Teach patients about acute symptoms that can occur and in what time frame; instruct patients to report symptoms promptly so the nurse can differentiate between cold-induced acute CIPN (reoccurs with each treatment) and hypersensitivity reaction (risk may increase with number of doses).  
• Avoid cold exposure and sudden chilling (e.g., reaching into a refrigerator or freezer, air conditioning in the summer, drinking ice-cold drinks, eating ice cream or other cold foods, cold shower), which can induce acute CIPN for five to seven days after treatment.  
• Wear gloves and a scarf when opening a refrigerator or going into a cold air-conditioned room.  
• During winter months, cover mouth with scarf, wear gloves, and have someone preheat car.  
• Identify and avoid triggers. With all agents associated with progressive peripheral neuropathy, enhance environmental safety.  
• Pay attention to lighting in rooms, halls, and walkways; use night lights or flashlights.  
• Install handrails where possible.  
• Use nonslip floors, avoid loose throw rugs, clear clutter, etc.  
• Altered ability to sense temperature: Turn water heater setting to low, use pot holders when cooking, etc.  
• Discuss the need for a disabled parking permit (requires medical prescription), which may become more important with progressive peripheral neuropathy.  
• Discuss the possible need for occupational or physical therapy (requires medical prescription). |
| Administer chemotherapy and adjunctive medical therapies. | Attempt to reduce the onset and severity of CIPN.                                                                                                                                                                                                                                               | • Discuss with prescriber the administration of IV or oral calcium and magnesium.  
• Assess for painful CIPN; consult with a prescriber regarding the potential benefit of adjuvant (anticonvulsant or antidepressant) and/or other analgesics, dependent on pain severity and characteristics.  
• Some clinicians also suggest a B complex vitamin supplement, based on information that B vitamin deficiencies may cause neuropathy. |

*Note.* Based on information from Almadrones, 2001; Almadrones & Arcot, 1999; Barharmand, 2004; Gamelin et al., 2002; Sorich et al., 2004; Sweeney, 2002; Wilkes, 2005.
If baseline assessment is normal, subsequent assessments should start with questions about new symptoms reflecting CIPN in the feet and hands. Evaluations should consider the general order of CIPN progression from unmyelinated or lightly myelinated, small sensory fibers to large, highly myelinated fibers (Polomano & Bennett, 2001). Neuropathic pain (burning, lancinating, or aching), dysesthesia, and decreased sensitivity to light touch, pinpricks, and temperature reflect damage to small, unmyelinated sensory fibers. Damage to large sensory fibers causes abnormalities in vibration and position sense and decreased deep tendon reflexes. Practical ways to assess for impaired fine movement of patients’ hands, particularly those who have paresthesia or dysesthesia, are to ask them to button their shirts, lace their shoes, pick up coins, or write a few sentences (Almadrones, 2001; Gamelin et al., 2002; Wilkes, 2005). Nurses also should ask patients at each chemotherapy visit about tingling, numbness, and difficult-to-describe pain. Assessments should continue after chemotherapy is stopped if patients received agents known to cause tingling.

Patient teaching is important for those at risk for acute or cumulative CIPN and creates an environment in which patients are likely to report symptoms and use self-care measures (Polomano & Farrar, 2006). Teaching for acute CIPN from oxaliplatin should include helping patients to identify their own triggers for cold-induced symptoms and reminding them that symptoms can persist for as long as seven days after chemotherapy (Almadrones, 2001; Barharmand, 2004; Wilkes, 2005). Symptom persistence and analgesic or antihistamine interventions after taxanes also should be stressed. Teaching patients about when cumulative CIPN can occur should include self-care measures to increase environmental safety and to avoid injury, such as adequate lighting and floors that are clear of clutter and throw rugs. In addition, patients’ temperature sensation may become impaired, so nurses should instruct them to stay focused on tasks, avoid or protect against extremes in temperature (e.g., wear gloves and socks in cold weather), use potholders when baking or cooking, use gloves when washing dishes, and turn down the temperature of a water heater (Almadrones & Arcot, 1999; Gamelin et al., 2002; Marrs & Newton, 2003; Sweeney, 2005). Several online sites may be useful sources of information to increase nurses’ knowledge or to assist patients experiencing CIPN (see Figure 4).

With oxaliplatin administration, nurses must determine whether a patient’s report of “difficulty breathing” is cold related (not a hypersensitivity reaction) or not (more likely hypersensitivity) (Gamelin et al., 2002). Cold-induced sensory reactions may be accompanied by pain or burning in the arm into which the drug is infusing and can occur after a few minutes of starting the infusion to as long as seven days after chemotherapy (Wilkes, 2005). Oxaliplatin should be room temperature when administered. Furthermore, prolonging the duration of infusion to six hours, encouraging patients to remain calm and drink a warm beverage, and providing a warm blanket are interventions that usually alleviate symptoms and prevent recurrence. Repeated peripheral doses of oxaliplatin can intensify pain and burning with administration and persist for hours to days after completion of infusion. Administration strategies that may reduce pain intensity include admixing oxaliplatin in 500 ml of a 5% dextrose solution, using the largest vein possible, and applying 1% hydrocortisone cream or warm compresses above the IV insertion site (Wilkes).

If pain occurs, analgesics may not only decrease discomfort but also enable patients to continue chemotherapy. In collaborating with physicians, nurses should remember that anticonvulsants or TCAs may be beneficial, as well as opioids for patients with severe neuropathic pain. Patient teaching definitely should include minimizing adverse effects from analgesics, such as prophylactic stool softeners plus laxatives to prevent opioid-induced constipation.

Nonpharmacologic interventions may benefit patients with painful CIPN, and other goals of care restore or maintain function, prevent deformity, and ensure patient safety (Gianfrocca et al., 2006). Other potentially helpful interventions for neuropathic pain include transcutaneous nerve stimulation, relaxation techniques, and exercise (Marrs & Newton, 2003). Referral to rehabilitation medicine or physical therapy may enhance the assessment and management of functional impairment and balance problems that can occur with CIPN (Wampler, Hamolsky, Hamel, Melisko, & Topp, 2005). Such professionals might suggest gentle low-impact aerobic exercise, orthotic devices, canes or walkers, pain desensitization with gentle compression to painful areas (e.g., wearing snug-fitting socks), massage, or whirlpool therapy starting with calm water. However, patients...
with allodynia may find massage painful and water temperature must be monitored, particularly in patients with major sensory loss who might be burned (Armstrong et al., 2005). Patients experiencing CIPN in the feet and lower legs may experience tripping or near falls, which can indicate risk for permanent foot drop (Cianfrocca et al.). Physical therapists can teach patients exercises they can do at home to stretch ankles and forefeet to prevent foot drop, as well as reinforce teaching about avoiding injuries.

**Summary**

The care of patients with cancer will become increasingly complex as new agents are identified and incorporated into new treatment regimens. In many instances, the new options have led to increased survival and the probability that patients will receive one or more neurotoxic chemotherapy drug. The medical and nursing issues in dealing with adverse effects such as CIPN are increasing in importance, as goals of chemotherapy consider QOL as well as the ability to continue chemotherapy and improve patient outcomes. Nurses must be diligent in the care of people at risk—that is, those receiving single and multiple neurotoxic chemotherapy regimens over an extended period. In addition, this is an exciting time for oncology nurses to be at the forefront in patient care that focuses on more effective therapeutic options to alleviate the underlying causes of and/or symptoms of CIPN (du Bois et al., 1999).

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**References**


