

FEATURE ARTICLE

Putting Evidence Into Practice[®]: Evidence-Based Interventions for Chemotherapy-Induced Peripheral Neuropathy

Constance Visovsky, PhD, RN, ACNP, Mary Collins, MSN, RN, OCN[®],
Linda Abbott, RN, MSN, AOCN[®], CWON, Julie Aschenbrenner, RN, BSN, OCN[®],
and Connie Hart, BSN, RN, OCN[®]



Chemotherapy-induced peripheral neuropathy (CIPN) continues to be a significant, debilitating symptom resulting from the administration of neurotoxic chemotherapy for the treatment of cancer. CIPN is an important consequence of cancer treatment because of its potential impact on physical functioning and quality of life. Oncology nurses play an important role in assessing, monitoring, and educating clients about CIPN. Despite investigations concerning pharmacologic and nonpharmacologic approaches to either preventing or minimizing the neurotoxicity resulting from certain chemotherapeutic agents, evidence to support the interventions is lacking. This article presents information concerning CIPN and summarizes the evidence for pharmacologic and nonpharmacologic approaches to the prevention and treatment of CIPN.

Chemotherapy-induced peripheral neuropathy (CIPN) is a significant, debilitating symptom directly related to the administration of neurotoxic chemotherapy for the treatment of cancer. CIPN compromises quality of life and results in pain or discomfort (Cavaletti & Zanna, 2002). Peripheral neuropathy is the end result of peripheral, motor, sensory, and autonomic neuron damage secondary to neurotoxic chemotherapy agents that inactivate the components required to maintain the metabolic needs of the axon (Postma & Heimans, 2000). Given the lack of standardized measurement and reporting mechanisms, the incidence of CIPN is relatively unknown. However, the incidence of severe CIPN has been estimated at 3%–7% in people treated with single agents, and upwards of 38% in those treated with multiple chemotherapeutic agents (Cavaletti & Zanna).

The chemotherapeutic agents most often associated with CIPN are platinum compounds, taxanes, vinca alkaloids, thalidomide, and bortezomib. CIPN is a concern for patients and clinicians, as manifestations of neurotoxicity can result in chemotherapy dose reductions, treatment delays, or discontinuation of treatment.

Although no standard therapy exists for the prevention or treatment of CIPN, nursing care can improve associated symptoms. A lack of consensus regarding assessment measurements and subsequent grading of CIPN makes comparisons among studies of CIPN difficult. Most assessments of CIPN reported in the literature used combinations of subjective symptom reports and objective clinical measurements. Figure 1 displays the most common characteristics of CIPN.

Search Strategy

This evidence-based review of interventions specifically aimed at the prevention or treatment of CIPN was drawn from an examination of the literature that included pilot studies, clinical trials, systematic reviews of the literature, and case studies. The Oncology Nursing Society Putting Evidence Into Practice[®] (PEP) CIPN Team consisted of two advanced practice nurses, two staff nurses, and a nurse researcher. The CIPN Team chose not to include animal model-based studies because applicability and generalizability to human populations has not been established. No meta-analyses addressing the prevention or treatment of CIPN were found in the literature. The team searched MEDLINE[®], the National Library of Medicine's database. Search terms included *chemotherapy-induced*

Constance Visovsky, PhD, RN, ACNP, is an associate professor in the College of Nursing at the University of Nebraska Medical Center in Omaha; Mary Collins, MSN, RN, OCN[®], is an advanced practice nurse at the Carle Clinic Cancer Center in Urbana, IL; Linda Abbott, RN, MSN, AOCN[®], CWON, is an advanced practice nurse in the Holden Comprehensive Cancer Center at the University of Iowa Hospitals and Clinics in Iowa City; Julie Aschenbrenner, RN, BSN, OCN[®], is a staff nurse in the blood and marrow transplant unit at the Holden Comprehensive Cancer Center; and Connie Hart, BSN, RN, OCN[®], is a clinical educator at the Carle Foundation Hospital in Urbana, IL. No financial relationships to disclose. (Submitted February 2007. Accepted for publication July 27, 2007.)

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Sensory Symptoms

Paresthesia
Hyperesthesia
Hypoesthesia
Dysesthesia
Pain
Numbness and tingling
Hyporeflexia or areflexia
Diminished or absent proprioception
Diminished or absent vibratory sensation
Diminished or absent cutaneous sensation
Diminished or absent sense of discrimination between sharp and dull

Motor Symptoms

Weakness
Gait disturbance
Balance disturbance
Difficulty with fine motor skills (e.g., buttoning clothing, writing)

Autonomic Symptoms

Constipation
Urinary retention
Sexual dysfunction
Blood pressure alterations

Figure 1. Characteristics of Chemotherapy-Induced Peripheral Neuropathy

peripheral neuropathy, peripheral neuropathy, and neuropathy. Search terms specific to known CIPN interventions also were explored, including *human leukemia inhibitory factor, nerve growth factor, neurotrophin-3, exercise and chemotherapy-induced peripheral neuropathy, exercise and neuropathy, diabetes and peripheral neuropathy, vitamin E, tricyclic antidepressants, amifostine, calcium/magnesium infusions, carbamazepine, glutathione, alpha lipoic acid, and glutamine.* Other search terms were *alternative therapy, complementary therapies, herbal therapies, plant-medicinal, herb(s), herbal(s), acupuncture, electric nerve stimulation, high-frequency external muscle stimulation, transelectrical nerve stimulation, spinal cord stimulation, anodyne therapy, pulsed infrared light therapy (PILT), social support, psychosocial support, educational interventions, patient education, patient safety, safety, injury, accidents, safety management, protective devices, and capsaicin.*

Because data regarding CIPN-specific interventions are limited, the team also explored the diabetes and HIV literature for evidence-based interventions for peripheral neuropathy and expanded the literature search beyond five years as appropriate. Once the team members obtained the articles, they reviewed and classified them by the Oncology Nursing Society PEP Weight of Evidence Classification System, which establishes six categories by strength of evidence: recommended for practice, likely to be effective, benefits balanced with harms, effectiveness not established, effectiveness unlikely, or not recommended for practice (see Table 1). All work by the CIPN team received external peer review by known experts in the field. The review is limited to interventions for the prevention and treatment of CIPN. Interventions specific to the treatment of neuropathic pain are not covered in this review.

Highlights of Reviewed Literature

At the present time, no nursing interventions for the prevention or treatment of CIPN can be categorized as recommended for practice or likely to be effective. Evidence from studies of the various pharmacologic and nonpharmacologic treatments reviewed failed to meet the scientific rigor necessary for practice recommendation. Although several systematic reviews have explored treatments to prevent, delay, or ameliorate CIPN, no meta-analyses have been conducted that can attest to a particular treatment benefit outweighing the potential for harm. Studies of pharmacologic and nonpharmacologic interventions with adequate sample sizes, rigorous study design, and standardized, well-established measurements of CIPN still are necessary.

Pharmacologic Interventions

In recent years, many pharmacologic agents have been tested for their efficacy in preventing or improving CIPN. Pharmacologic agents such as chemoprotectants, vitamins, electrolyte infusions, amino acids, tripeptides, neurotrophic factors, antidepressants, anticonvulsants, and certain cytokines and carnitines have been the focus of recent research efforts. Currently, no evidence supports the use of pharmacologic interventions for patients experiencing CIPN. Effectiveness of pharmacologic agents to prevent or treat CIPN has not been established.

To obtain the most up-to-date evidence, the Oncology Nursing Society PEP CIPN Team reviewed pharmacologic studies specifically aimed at the prevention or treatment of CIPN and published in the previous five years. The search was expanded when no published research was found within the five-year timeframe. The literature clearly shows that pharmacologic agents have met with limited success in preventing or resolving CIPN in patients with cancer.

Chemoprotectants: Amifostine, an organic thiosulfate, is dephosphorylated in tissues to an active thiol metabolite (Hilpert et al., 2005). In the active form, amifostine detoxifies chemotherapy drugs and facilitates DNA repair while not interfering with the efficacy of chemotherapy. Three studies examined the effect of amifostine on peripheral neuropathy outcomes associated with taxane-based chemotherapy regimens (Hilpert et al.; Moore et al., 2003; Openshaw et al., 2004). In all three studies, no differences were found in sensory or motor neurotoxic symptoms in patients treated with amifostine. Amifostine also was found to be ineffective in preventing or reducing the neurotoxic effects of high-dose paclitaxel. Researchers have hypothesized that because the cytoprotective effect of amifostine occurs at the DNA level, it cannot prevent paclitaxel-induced neurotoxicities that occur with microtubular aggregation.

Vitamin E: As an antioxidant, vitamin E is believed to protect against cellular oxidative damage and side effects such as numbness, tingling, burning, and pain in peripheral extremities produced by cisplatin and other cytotoxic drugs (Weijl et al., 1998). Three studies examined the cytoprotective effect of vitamin E supplementation on the development of CIPN following the administration of cisplatin, paclitaxel, or a combination regimen (Argyriou et al., 2005; Bove, Picardo, Maresca, Jandolo, & Pace, 2001; Pace et al., 2003). In two studies, participants were randomized to receive either 300 mg or 600 mg of vitamin E during

Table 1. Putting Evidence Into Practice® Weight-of-Evidence Classification Schema

WEIGHT-OF-EVIDENCE CATEGORY	DESCRIPTION	EXAMPLES
Recommended for practice	Effectiveness is demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews. Expected benefit exceeds expected harms.	At least two multisite, well-conducted, randomized, controlled trials (RCTs) with at least 100 subjects Panel of expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence
Likely to be effective	Evidence is less well established than for those listed under recommended for practice.	One well-conducted RCT with fewer than 100 patients or at one or more study sites Guidelines developed by consensus or expert opinion without synthesis or quality rating
Benefits balanced with harms	Clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities.	RCTs, meta-analyses, or systematic reviews with documented adverse effects in certain populations
Effectiveness not established	Data currently are insufficient or are of inadequate quality.	Well-conducted case control study or poorly controlled RCT Conflicting evidence or statistically insignificant results
Effectiveness unlikely	Lack of effectiveness is less well established than those listed under not recommended for practice.	Single RCT with at least 100 subjects that showed no benefit No benefit and unacceptable toxicities found in observational or experimental studies
Not recommended for practice	Ineffectiveness or harm clearly is demonstrated, or cost or burden exceeds potential benefit.	No benefit or excess costs or burden from at least two multisite, well-conducted RCTs with at least 100 subjects Discouraged by expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence

Note. Based on information from Mitchell & Friese, n.d.

cisplatin chemotherapy and for three months after the completion of chemotherapy; a control group did not receive vitamin E supplementation (Argyriou; Pace et al.). Clinical and neurophysiologic examinations assessed neurotoxicity. Both studies reported the incidence of neurotoxicity to be lower in the groups who received vitamin E supplementation as compared to the control group.

Symptoms of CIPN and vitamin E deficiency prompted Bove et al. (2001) to measure vitamin E in the plasma of five patients (group 1) who developed peripheral neuropathy after six cycles of treatment with cisplatin and in the plasma of five patients (group 2) before and after two to four cycles of cisplatin. Results indicated that plasma levels of vitamin E were decreased in group 1. Additionally, the plasma levels of vitamin E in group 2 were significantly lower after two to four cycles of cisplatin as compared to pretreatment levels. The small pilot study suggests a relationship between cisplatin neurotoxicity and vitamin E deficiency. Randomized clinical trials with larger sample sizes are needed to further evaluate the role of vitamin E in the prevention and treatment of CIPN.

Calcium and magnesium infusions: Oxalate, an oxaliplatin metabolite, seeks and binds to calcium and magnesium (Gamelin et al., 2004). The process may be responsible for the neurotoxic effects of oxaliplatin therapy. The efficacy of calcium and magnesium infusions as possible treatment for CIPN was tested in a small sample of patients who developed acute neurotoxic symptoms after receiving oxaliplatin. Following infusion of calcium and magnesium, patients experienced improvements in pseudolaryngospasm and other clinical manifestations of acute neurotoxicity (Gamelin et al.). The same investigators tested

calcium and magnesium infusions as a means of preventing neurotoxicity associated with oxaliplatin. Ninety-six patients with advanced colorectal cancer received 1 g of both calcium gluconate and magnesium sulfate before and immediately after oxaliplatin infusion. At the end of oxaliplatin therapy, 65% of the patients in the infusion group had no symptoms of neuropathy as compared to only 37% in the control group (Gamelin et al.). However, the studies used a retrospective, nonrandomized study design. Evidence from randomized, controlled clinical trials is necessary before calcium and magnesium infusions can be recommended for the prevention or treatment of CIPN.

Tricyclic antidepressants: Nortriptyline, the active N-demethylated metabolite of amitriptyline, blocks the reuptake of serotonin and norepinephrine in the pain-modulating system in the central nervous system (Hammack et al., 2002). Tricyclic antidepressants exert analgesic effects in the treatment of CIPN; relief of neuropathic symptoms, particularly paresthesias, also has been explored. A randomized, double-blind, placebo-controlled, crossover study was conducted with 51 patients treated with cisplatin who received escalating doses of nortriptyline up to 100 mg per day over a four-week period. Questionnaires concerning pain, sleep, quality of life, and neuropathic symptoms indicated a relatively modest benefit in cisplatin-induced paresthesias over the placebo group. That one small pilot study, which lacked objective measurements of neuropathy, does not establish the effectiveness of nortriptyline in reducing neuropathy-associated paresthesias.

Anticonvulsants: Carbamazepine, an anticonvulsant drug that slows the rate of recovery of voltage-activated sodium

channels, seems to protect against oxaliplatin-induced neurotoxicity. Carbamazepine was tested in the prevention of CIPN in one nonrandomized pilot study consisting of 10 previously treated patients with advanced colorectal cancer receiving oxaliplatin, folinic acid, and 5-fluorouracil. Carbamazepine 200–600 mg was administered orally, with doses adapted to serum levels of 3–6 mg/L. Vibration sensation of the palmar surfaces of the hands and feet and subjective reports of cold-induced symptoms were assessed weekly. World Health Organization (WHO) grade 2–4 neuropathy was absent in the patients treated with carbamazepine, as compared to 30% who experienced grade 2–4 neuropathy in a historical control group (Eckel et al., 2002). Further randomized, placebo-controlled trials are necessary to determine whether carbamazepine can be used to prevent or treat CIPN.

Acetyl-L-carnitine: Only two small studies examined the use of acetyl-L-carnitine for CIPN. The studies tested the effectiveness of acetyl-L-carnitine in the treatment of preexisting paclitaxel- or cisplatin-induced peripheral neuropathy. Acetyl-L-carnitine was administered as 1 g via IV daily for 10 consecutive days or 1 g by mouth three times daily for eight weeks to individuals who had established paclitaxel- or cisplatin-induced peripheral neuropathy (Bianchi et al., 2005; Maestri et al., 2005). Assessment of neuropathy symptoms, toxicity grading scales for neuropathy, and neurologic and electrophysiologic assessments were performed before and after treatment with acetyl-L-carnitine. The studies were limited by small sample sizes and nonrandomized one-group designs. Randomized clinical trials are necessary before acetyl-L-carnitine can be recommended as a potential treatment for CIPN.

Glutamine: Glutamine, a neutral gluconeogenic nonessential amino acid, is thought to have neuroprotective effects for patients receiving paclitaxel (Stubblefield et al., 2005). Glutamine has been shown to upregulate nerve growth factor in animal models and may have a similar action in humans (Vahdat et al., 2001). In an attempt to reduce CIPN from high-dose paclitaxel, Vahdat et al. treated 12 women with advanced breast cancer with glutamine 10 g daily for four days starting 24 hours after completion of paclitaxel. The researchers then compared neurologic findings to 33 women who did not receive glutamine. Neurologic examinations, nerve conduction studies, and symptom assessments were performed prior to paclitaxel administration and two weeks after therapy was completed. Results indicated that study participants who received glutamine had fewer symptoms, with only 8% of women reporting dysesthesias in the fingers and toes, as compared to 40% of the women who did not receive glutamine.

Stubblefield et al. (2005) examined the neuroprotective effect of glutamine on 46 patients scheduled to receive high-dose paclitaxel prior to stem cell transplantation. Seventeen patients received 10 g of glutamine three times daily for a total of four days beginning 24 hours after completion of paclitaxel. The remaining 29 patients made up the control group. Results of neurologic symptom questions and electrodiagnostic testing indicated that those who received glutamine developed less weakness, loss of vibratory sensation, and toe numbness as compared to the control group. Larger, randomized, placebo-controlled trials are necessary to assess the efficacy of glutamine for the prevention of CIPN.

Glutathione: Glutathione, a naturally occurring thiol tripeptide, may prevent neurotoxicity induced by platinum compounds by hampering the initial accumulation of platinum adducts in the dorsal root ganglia (Ocean & Vahdat, 2004). Three studies testing the potential neuroprotective effects of glutathione have been published. In a randomized, double-blind, placebo-controlled trial, 52 individuals with advanced colorectal cancer scheduled to receive oxaliplatin every two weeks for 4–12 cycles were randomized to receive glutathione 1,500 mg/m² by IV infusion (n = 26) or a placebo infusion of normal saline (n = 26) prior to receiving oxaliplatin. Neurologic examinations, including measurements of strength and reflexes, assessment of neurologic symptoms, examination of position and vibratory sensation, and neurophysiologic evaluations of sural nerves, were conducted at baseline and at the fourth, eighth, and twelfth cycles of chemotherapy. Following all cycles of chemotherapy, the incidence of neuropathy was greater in those in the placebo group as compared to those who received glutathione. None of the patients who received glutathione experienced grade 3–4 neurotoxicity, whereas five participants who received placebo (26%) experienced grade 3–4 neurotoxicity. No changes were noted in sural nerve mean latency or sensory amplitude potential (SAP) after treatment with glutathione, whereas those who received placebo infusions experienced significant declines in SAP. Based on the preliminary data, the authors concluded that glutathione may be effective for reducing the signs and symptoms of peripheral neuropathy (Cascinu et al., 2002).

Smyth et al. (1997) examined the potential neuroprotective effects of glutathione in a sample of 151 women with ovarian cancer who were randomized to receive cisplatin with or without glutathione. Seventy-seven women received a placebo and 74 received glutathione 3 g/m² every three weeks for six cycles. Audiograms and neurologic assessments were performed at baseline and after three and six cycles of therapy. More patients who received glutathione (58%) than placebo (39%) were able to receive the full six cycles of cisplatin. Women in the glutathione arm had a statistically significant 2 kg rise in weight over the course of the study (p = 0.01). Women in the study who received glutathione reported an improvement in quality of life, as evidenced by fewer depressive symptoms and better mood during cisplatin chemotherapy.

A double-blind, placebo-controlled trial assessed the efficacy of glutathione in preventing CIPN in 50 chemotherapy-naive patients with advanced gastric cancer undergoing treatment with cisplatin-based combination chemotherapy. Twenty-five study participants in the experimental group received an infusion of glutathione 1.5 g/m² before each weekly cisplatin treatment and by intramuscular injection on days 2 and 5, whereas the 25 control group participants received placebo infusions of normal saline. Researchers performed neurologic examinations of strength, deep tendon reflexes, neuropathy symptoms, vibration, and position sensation, as well as neurophysiologic assessment of the medial, ulnar, and sural nerves. After nine weeks, no one who received glutathione had clinical evidence of neuropathy, as opposed to 66% in the placebo group. By week 15, four participants in the glutathione arm (17%) showed clinical evidence of neurotoxicity, compared to 16 in the placebo arm (88%). No changes in SAP were noted in those who received glutathione. However, SAP was significantly affected

in those who received placebo infusions (Cascinu, Cordella, Del Ferro, Fronzoni, & Catalano, 1995). Further randomized clinical trials are needed to test the effectiveness of glutathione as an intervention for CIPN.

Alpha lipoic acid: Although no studies have reported on the use of alpha lipoic acid in the oncology population, it has shown some benefit in the treatment of diabetic polyneuropathy. A meta-analysis of four randomized, double-blind, placebo-controlled trials including 1,258 patients with diabetic polyneuropathy demonstrated that treatment with alpha lipoic acid 600 mg per day via IV resulted in clinically significant improvements in pain, burning, paresthesias, and numbness (Ziegler, Nowak, Kempler, Vargha, & Low, 2004). Further study is needed to determine the safety and efficacy of alpha lipoic acid in the prevention and treatment of CIPN.

Human leukemia factor: Only one study tested recombinant human leukemia factor (rhuLIF) in a human population (Davis et al., 2005). One hundred seventeen participants were enrolled into the phase II, double-blind, placebo-controlled clinical trial. Study participants were randomized to one of three study arms: rhuLIF 2 ug/kg (n = 36), rhuLIF 4 ug/kg (n = 39), or placebo (n = 42). Neurologic assessments consisting of peripheral nerve electrophysiology testing of sensory and motor nerves, vibration threshold, and neurologic signs and symptoms were obtained prior to rhuLIF administration, after the fourth and last cycles of chemotherapy, and at three months after chemotherapy. Study results failed to show evidence that rhuLIF prevented, delayed, or diminished peripheral neuropathy. No plans have been made to continue development of rhuLIF for the prevention or treatment of peripheral neuropathy (Davis et al.).

Nonpharmacologic Interventions

Effectiveness has not been established for many nonpharmacologic interventions for the prevention or treatment of CIPN. Interventions with insufficient data or data of inadequate quality are included in this review. Because of a lack of studies focused specifically on CIPN, the authors also evaluated studies of nonpharmacologic approaches in diabetes- or HIV-induced peripheral neuropathy.

Acupuncture: The team reviewed five studies that used acupuncture for the treatment of peripheral neuropathy resulting from chemotherapy, diabetes, or HIV. Only one small case study (Wong & Sagar, 2006) reported the use of acupuncture specifically for CIPN. Five consecutive patients (60–71 years old, with greater than WHO grade II CIPN symptoms and advanced gynecologic cancers treated with carboplatin and paclitaxel) were given acupuncture treatment once a week for six weeks followed by four weeks of rest and then a second course of acupuncture for six additional weeks. Gait improved significantly in the three patients with balance disturbances. Following acupuncture treatment, the five patients experienced improvement in sensation, gait, and balance and had decreased analgesic dosages. Some control of symptoms (pain, numbness, and tingling of fingers and toes) was obtained after the first treatment. No adverse side effects occurred, and the benefits of acupuncture were maintained for six months for four of the five patients involved.

Acupuncture also has been studied in diabetic and HIV populations with mixed results. In one randomized, controlled trial,

a population of diabetic patients with peripheral neuropathy experienced a significant improvement in nerve conduction velocities. Ninety individuals with diabetic peripheral neuritis were randomized equally to one of three groups: wrist-ankle acupuncture, body acupuncture, or routine Western medical treatment (control), which included vitamin B₁ and B₁₂ injections daily for three seven-day courses with two-day breaks between courses. The therapeutic benefits of improved blood sugar, blood viscosity, lipid levels, and peripheral nerve function obtained with wrist-ankle acupuncture was superior to the Western medicine group; however, no differences were found between the two acupuncture groups (Jiang, Shi, Li, Zhou, & Cao, 2006).

In a study by Abuaisha, Costanzi, and Boulton (1998), 46 individuals with chronic and painful diabetic neuropathy received six courses of classic acupuncture analgesia using traditional Chinese acupuncture points over 10 weeks. Seventy-seven percent (n = 34) of the participants who completed the study showed improvement in subjective pain and sleep. Participants were followed for 18–52 weeks. Sixty-seven percent of participants reported stopping or reducing their pain medications, but only 21% reported complete resolution of pain. Only 24% (n = 8) required further acupuncture treatments beyond the initial six courses. No significant changes were found in peripheral neurologic examination scores, vibration perception thresholds, or glycosylated hemoglobin (HbA1c) (Abuaisha et al.).

One randomized, controlled trial in a population of patients with HIV and peripheral neuropathic pain (n = 250) found no significant improvements in pain scores with the use of acupuncture or amitriptyline over a control group (Shlay et al., 1998). A study using a pre-/post-treatment design examined the effects of acupuncture on 21 people with HIV-related peripheral neuropathy; the researchers found that pain and symptoms of peripheral neuropathy were reduced during the period of acupuncture treatment (Phillips, Skelton, & Hand, 2004). No studies employing acupuncture as an intervention have noted any risks or hazards associated with the treatment. The relatively small sample sizes, mixed clinical populations, varied assessments of the effectiveness of acupuncture, and lack of studies in oncology populations clearly point to the need for further research into the use of acupuncture for the treatment of CIPN.

Assistive devices: No studies have examined the use of assistive device in an oncology population. However, two small studies have examined the use of a cane alone or in combination with orthotics in diabetes populations (Ashton-Miller, Yeh, Richardson, & Galloway, 1996; Richardson, Thies, DeMott, & Ashton-Miller, 2004). Healthcare professionals generally refer clients with CIPN to a physical therapist for a cane, orthotic braces, or a splint to assist with lower-extremity alignment and balance. Although the use of assistive devices does not directly reduce the effects of peripheral neuropathy, some patients find them beneficial and they may help to prevent injury from sensory and motor changes.

Physical activity and exercise: Physical activity and exercise interventions have not been studied in the prevention or treatment of peripheral neuropathy in patients with cancer. Three studies with small sample sizes have examined progressive resistance exercise, aerobic exercise, and stretching exercises in the treatment of diabetic peripheral neuropathy and

myotonic dystrophy. All three found significant improvements in outcomes such as stance, functional reach, and peroneal and sural motor nerve conduction velocity (Balducci et al., 2006; Lindeman et al., 1995; Richardson, Sandman, & Vela, 2001). However, the studies had major flaws, so the findings should be interpreted with caution. Further randomized clinical trials are needed with oncology populations.

A Cochrane review (White, Pritchard, & Turner-Stokes, 2004) examined the role of exercise for individuals with peripheral neuropathy from etiologies other than chemotherapy. Trials in the review included any form of exercise therapy, such as progressive resistance exercise (isometric, isotonic, or isokinetic) and/or endurance training, compared with either no exercise or an alternative form of nondrug treatment. Three identified trials included 82 patients with peripheral neuropathy of hereditary, inflammatory, or metabolic etiology. The primary outcome was functional ability at a timeframe less than eight weeks after the start of the intervention/control period. Secondary outcomes were muscle strength, endurance, psychological status or quality of life, and return to work. In addition, unfavorable secondary outcomes were assessed, including increased neurologic deficits and pain sufficient to require analgesics. Results of the included trials failed to show any effect of strengthening and endurance exercise programs on functional ability in people with peripheral neuropathy. However, evidence is emerging that strengthening exercise programs are moderately effective in reversing losses in muscle strength related to peripheral neuropathy. None of the trials fulfilled all of the criteria for methodologic quality.

Pulsed infrared light therapy: PILT, also called anodyne therapy, has not been studied in oncology populations. PILT consists of delivering infrared light in an effort to improve foot perfusion by stimulating nitric oxide production. It is delivered by a machine, which patients can rent or purchase. Only three studies were found that used PILT in diabetic patients with diagnosed peripheral neuropathy. Of those studies, only one used a randomized, blinded clinical trial design. Leonard, Farooqi, and Myers (2004) conducted a double-blind, randomized, placebo-controlled study of 27 people with diabetic peripheral neuropathy. Significant improvements in sensation, neuropathic symptoms, and pain were found for most participants, with the exception of those with the most severe neuropathy scores. One study (n = 27) found anodyne therapy to be a safe and effective treatment that improved sensory impairments as measured by peroneal nerve function and current perception thresholds in 26 participants after 10 treatments delivered over two weeks, each lasting 40 minutes (Prendergast, Miranda, & Sanchez, 2004). Arnall et al. (2006) studied 22 subjects with diabetic peripheral neuropathy. PILT treatments were given for 30 minutes three times a week over an eight-week period. Significant improvements in sensation as measured by Semmes-Weinstein monofilaments were found. The finding held even for those with long-standing, profound diabetic peripheral neuropathy. Although no study of PILT demonstrated risks associated with the treatment, the small sample sizes, lack of oncologic study populations, and nonrandomized study designs used in two of the three studies fail to provide adequate evidence to recommend the use of anodyne therapy in CIPN.

Transcutaneous nerve stimulation: Transcutaneous nerve stimulation (TENS) and high-frequency external muscle

stimulation have elicited some benefits in diabetic patients with peripheral neuropathy but have not been investigated in an oncology population. In a randomized clinical trial, Forst et al. (2004) compared TENS with an electrically inactive device in 19 participants with diabetic neuropathy. Significant subjective improvements in neuropathy symptoms of numbness, lancinating pain, prickling sensations, and allodynia were demonstrated in 70% of treatment group participants as compared to 29% of control group participants. Reichstein, Labrenz, Ziegler, and Martin (2005) compared TENS with high-frequency external muscle stimulation in a sample of 41 diabetics. In the study, high-frequency muscle stimulation was more effective than TENS in relieving lower-extremity pain; however, both were effective in decreasing symptoms of numbness, burning, paresthesia, and dyesthesia. Only one patient reported muscular discomfort associated with high-frequency external muscle stimulation. Improvements in neuropathy symptoms were short lived; study participants reported recurrence of symptoms after several days.

Capsaicin ointment: To date, no studies have examined the effects of capsaicin ointment in the treatment of CIPN. Only one nonrandomized study of 13 diabetic patients with symptomatic, symmetrical peripheral neuropathy was conducted. In that study, one foot of each study participant was treated topically with 0.05% capsaicin ointment three to four times a day over an eight-week period. The contralateral foot of each participant remained untreated. Ten patients completed the study. A significant decrease in hypoesthesia was found in the capsaicin-treated feet, whereas no significant changes occurred in the control foot of each participant. Two patients discontinued treatment because of local erythema at the application site or generalized allergic skin reactions. For both participants who experienced skin effects, the effects disappeared after they discontinued the capsaicin ointment (Forst et al., 2002). The lack of studies using capsaicin ointment as a potential treatment in any population, specifically in an oncology population; the small sample size; and the lack of randomized trials prevent recommendation of capsaicin ointment in the treatment of CIPN.

Spinal cord stimulation: Spinal cord stimulation involves the surgical placement of leads in the epidural space to transmit pulsed energy across the spinal cord or near the desired nerve roots to control pain. It is based on the gate control theory. Spinal cord stimulation cannot be recommended for practice at this time. Only one case study was found in the literature; it reported the use of spinal cord stimulation for two patients with painful CIPN. Although the investigators reported improvements in pain, sensation, gait, and flexibility and a concurrent reduction in analgesic medication use when spinal cord stimulation was applied 6–18 hours per day, the high surgical risks and costs associated with the intervention must be weighed carefully against anticipated benefits (Cata et al., 2004).

Currently, the only interventions that can be recommended for nursing practice are education and support to preserve client safety (Almadrones & Arcot, 1999; Armstrong, Almadrones, & Gilbert, 2005; Marrs & Newton, 2003; Paice, 2007) (see Appendix).

- Teach clients the signs and symptoms of peripheral neuropathy and to report them to their healthcare providers as soon as they or their families notice them.

- Teach clients strategies for managing personal safety, such as using visual input to compensate for loss of lower-extremity sensation in navigating changing terrains.
- Teach clients the principles of foot care, including visual inspection of the feet for injury and the importance of wearing properly fitted shoes.
- Teach clients about the risk for ischemic and thermal injuries resulting from loss of sensation in extremities. Patients should protect body parts from cold and hot temperature extremes.
- Teach strategies to manage symptoms of autonomic dysfunction (postural hypotension, constipation, and urinary retention), such as dangling the legs prior to standing and maintaining a high-fiber diet and adequate fluid intake.

Summary

CIPN remains a significant problem for patients receiving chemotherapy for cancer. At present, no interventions for CIPN can be recommended for practice. No rigorously designed studies, meta-analyses, or systematic reviews support any of the interventions discussed, and risk of harm may outweigh potential benefits.

The study designs frequently were quasiexperimental in nature, thus used comparison groups as opposed to true control groups. The measurement tools employed to determine the presence or absence of CIPN were problematic. Many studies relied on neurologic examination techniques, which can vary from examiner to examiner, making suspect the equivalence of clinical findings. Additionally, the instruments used to grade CIPN varied; some studies relied on toxicity scales such as the National Cancer Institute's Common Terminology Criteria for Adverse Events, and others used the WHO classification. The lack of standardized instruments to measure the presence or absence of CIPN makes comparison of study findings difficult. Lastly, the studies in oncology populations tended to follow CIPN development throughout chemotherapy administration, but few studies had long-term follow-up of CIPN symptoms or clinical manifestations. The studies reviewed also contained small numbers of participants. The sample sizes in CIPN intervention studies became even smaller as participants dropped out because of increased symptoms, disease progression, or death. Studies testing the efficacy of interventions aimed at preventing or treating CIPN require adequate sample sizes to have enough statistical power to detect differences between those who receive a particular test treatment and those who do not. Interventions for the prevention and treatment of peripheral neuropathy have been tested primarily in diabetes populations. Few studies of pharmacologic and nonpharmacologic interventions have focused exclusively on oncology populations. When an oncology population was used to test a promising CIPN intervention, the study sample was made up of individuals with advanced cancers only. Lastly, studies lacked sufficient details concerning procedures. Studies of nonpharmacologic interventions in particular lacked specifics regarding how treatments were applied and the exact doses received; therefore, replicating the studies to confirm or refute findings is difficult.

Symptoms resulting from cancer and treatments can be influenced by nursing care (Given & Sherwood, 2005). To advance

the science regarding effective prevention and treatment strategies for CIPN, rigorously designed randomized clinical trials using appropriate oncology populations, adequate sample sizes, standard measurement procedures, and longitudinal follow-up of outcome measures are needed.

Author Contact: Constance Visovsky, PhD, RN, ACNP, can be reached at cvisovsky@unmc.edu, with copy to editor at CJONEditor@ons.org.

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Receive continuing nursing education credit for reading this article and taking a brief quiz. See the Continuing Nursing Education in this issue for more information.

Put Evidence Into Practice

The Putting Evidence Into Practice® (PEP) resource card for chemotherapy-induced peripheral neuropathy (CIPN) appears on the following pages. For more information about evidence-based interventions for CIPN, including different versions of the card, definitions, evidence tables, and a complete list of references, visit www.ons.org/outcomes/volume2/peripheral.shtml. PEP resources for several other nursing-sensitive patient outcomes are available at www.ons.org/outcomes.

The *Clinical Journal of Oncology Nursing* wants to hear how you use the PEP resources to improve the quality of cancer care that you deliver. E-mail CJONEditor@ons.org to share your experiences with nurses everywhere.

Appendix. Putting Evidence Into Practice® Card on Chemotherapy-Induced Peripheral Neuropathy

What interventions are used to prevent or reduce the effects of peripheral neuropathy for people with cancer?

RECOMMENDED FOR PRACTICE

Interventions for which effectiveness has been demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews and for which expectation of harms is small compared with the benefits

- There are no interventions that can be recommended for nursing practice as of December 30, 2006.

LIKELY TO BE EFFECTIVE

Interventions for which there is evidence from a single rigorously conducted controlled trial, consistent evidence from well-designed controlled trials using small samples or from meta-analyses/systematic reviews using small samples, or evidence from guidelines developed from evidence and supported by expert opinion

- There are no interventions likely to be effective for nursing practice as of December 30, 2006.

BENEFITS BALANCED WITH HARMS

Assistive Devices

No studies have been done of assistive device use in the cancer population. However, two small, nonrandomized studies of cane and orthotic use were done in the diabetes population that showed benefits, including prevention of foot drop and improvement in balance and proprioception.^{1,2}

- Although the use of assistive devices will not directly reduce the effects of peripheral neuropathy, some patients may find them beneficial.
- Healthcare professionals should refer clients to a physical therapist for a cane, orthotic braces, or a splint to assist with lower-extremity alignment and balance.
- Referral to a professional who is familiar with these devices and has the ability to educate patients on their use is recommended.

EFFECTIVENESS NOT ESTABLISHED

Interventions for which there are currently insufficient or conflicting data or data of inadequate quality

Carbamazepine

In a nonrandomized pilot study, 40 pretreated patients who received oxaliplatin were studied.¹⁰ Ten of these patients also received carbamazepine 200–600 mg orally daily (titrated to serum levels of 3–6 mg/L) just prior to and throughout treatment of oxaliplatin.

- No grade 2–4 peripheral neuropathy, according to the World Health Organization scale, occurred in any patient.¹⁰

Prevention Interventions

Acetyl-L-Carnitine

Only two small studies (nonrandomized, one-group design) of patients treated with acetyl-L-carnitine for chemotherapy-induced peripheral neuropathy were found.^{3,4}

- One gram IV/day for 10 consecutive days or 1 g by mouth tid for 8 weeks was used for prevention of paclitaxel- or cisplatin-induced peripheral neuropathy.^{3,4}

Alpha-Lipoic Acid

No studies have been done using alpha-lipoic acid in the oncology population, but some evidence exists of benefit in diabetic polyneuropathy.⁵

- A meta-analysis of four trials comprising 1,258 patients with diabetic polyneuropathy demonstrated that treatment with alpha-lipoic acid (600 mg/day IV) Monday through Friday for three weeks improved the chief symptoms of diabetic polyneuropathy to a clinically meaningful degree.⁵

Amifostine

Three studies have tested amifostine in prevention of chemotherapy-induced neurotoxicity.⁶⁻⁸

- Two of these studies have not shown amifostine to be effective in preventing or reducing symptoms of peripheral neuropathy.^{6,7}
- A prospective, double-blind, randomized, placebo-controlled trial was performed.⁸ Patients with advanced ovarian cancer received carboplatin/paclitaxel-based chemotherapy and were pretreated with amifostine 740 mg/m² versus placebo. Assessments included a questionnaire, the Common Terminology Criteria for Adverse Events (CTCAE), vibration threshold measurements, and quality of life. Results indicated that amifostine improved sensory neuropathy according to the National Cancer Institute CTCAE with regard to objective neurologic assessment, but almost no differences occurred in self-reported sensory or motor symptoms.⁸

Calcium and Magnesium

One nonrandomized, retrospective study suggested that calcium and magnesium given IV over 15 minutes before and after administration of oxaliplatin may decrease the incidence and intensity of peripheral neuropathy in patients.⁹

- Results indicated that only 4% of patients who received calcium/magnesium withdrew from treatment because of the neurotoxic effects of oxaliplatin, whereas 31% of patients withdrew in the control group. At the end of treatment, 20% of the patients who received calcium/magnesium had neuropathy, whereas 45% of patients who did not receive calcium/magnesium infusions developed neuropathy.⁹
- The researchers stated that a prospective, multicenter, double-blind, randomized, placebo-controlled trial is under way to determine the impact of calcium/magnesium on the neurotoxic effects of oxaliplatin.⁹

Glutamine

Glutamine 10 mg by mouth tid beginning 24 hours after chemotherapy and continuing for four days has been reviewed as a neuroprotective agent in chemotherapy-induced peripheral neuropathy.^{11,12}

- Results of two small, nonrandomized, nonplacebo-controlled studies indicate that some signs and symptoms of chemotherapy-induced peripheral neuropathy may be reduced by glutamine with paclitaxel-containing regimens. The neurologic assessments seemed to be a better indicator of signs and symptoms than nerve conduction studies.^{11,12}

Glutathione

Studies investigating glutathione as a neuroprotective agent in the oncology population are dated and do not demonstrate a clear benefit with its use.¹³⁻¹⁵

- The studies question whether it actually prevents toxicities or only delays them.¹³⁻¹⁵
- According to one study, glutathione may have some benefit in reducing signs and symptoms of peripheral neuropathy.¹³

Nortriptyline

One small study revealed modest improvement at best with nortriptyline over placebo for preventing cisplatin neurotoxicity.¹⁶

Recombinant Human Leukemia Inhibitory Factor (rhILF)

One study in patients receiving carboplatin/paclitaxel and rhILF (2–4 mcg/kg) concluded that no evidence supported that rhILF prevented, delayed, or diminished peripheral neuropathy.¹⁷ There are no future plans to continue development of rhILF for the prevention or treatment of peripheral neuropathy.¹⁷

Vitamin E

Two pilot studies^{18,19} and one small randomized study²⁰ showed some benefit to using oral vitamin E with cisplatin regimens. However, standard doses have not been determined, and more randomized controlled clinical trials are needed to further evaluate the neuroprotective effects of vitamin E.

Treatment Interventions

Acupuncture

Only one small case series study has been done on the use of acupuncture for chemotherapy-induced peripheral neuropathy.²¹ Acupuncture improved sensation and movement and resulted in decreased analgesic dosages for the five patients involved. Gait also was improved, and no adverse effects were noted. Control of symptoms persisted for six months for four of the five patients treated.

- Acupuncture also has been studied in the diabetic and HIV populations, with some mixed results.²²⁻²⁵
- None of the studies employing acupuncture identified any risks or hazards associated with the treatment.

Capsaicin

This therapy has not been studied in the oncology population. Capsaicin has been studied for the treatment of peripheral neuropathy in the diabetic population, with inconclusive results that prevent recommendation at this time.²⁶

- Ten patients completed the study with significant decreases found in the total symptom score of the capsaicin-treated arm and no significant changes occurring in the control feet. Two patients in this study discontinued treatment because of adverse events related to the treatment.²⁶

Physical Activity/Exercise

Physical activity/exercise interventions have not been studied in the prevention or treatment of peripheral neuropathy in patients with cancer.

- Three studies with small sample sizes have examined progressive resistance exercise, aerobic exercise, and stretching exercises in the treatment of diabetic peripheral neuropathy and myotonic dystrophy.^{2,27-29}
- All three studies found significant improvement in stance, functional reach, and peroneal and sural motor nerve conduction velocity. These studies contain findings that need to be interpreted with caution, as these studies have not been replicated in patients with cancer.^{2,27-29}

Pulsed Infrared Light Therapy (PILT) (also called anodyne therapy)

This therapy has not been studied in the oncology population. Three studies in the diabetic population were reviewed.³⁰⁻³³ Only one study was a randomized clinical trial.³⁰

- One study identified an improvement in sensation, neuropathy symptoms, and pain.³⁰ Those with the most severe neuropathy scores on entry into the study, however, did not show significant improvement in these symptoms.
- Two other studies also found improvement in sensation when using anodyne therapy in diabetic patients with peripheral neuropathy.^{31,32}
- None of the studies using PILT demonstrated any risks associated with the treatment.

Spinal Cord Stimulation

Use of spinal cord stimulation in two patients with chemotherapy-induced peripheral neuropathy was reported in one case study.³³

- Improvement in pain scores, gait, flexibility, and sensation scores and reduction in the use of analgesic medications were found with the use of the stimulator for 6–18 hours a day.³³
- Because surgical risks and costs are associated with this intervention, it is not recommended for practice at this time.³³

Transcutaneous Nerve Stimulation (TENS) and/or High-Frequency (HF) External Muscle Stimulation

These therapies have not been investigated in the oncology population, but limited studies have been done in the diabetic population with peripheral neuropathy. TENS has demonstrated some benefit in the treatment of diabetic peripheral neuropathy.^{26,34}

- One study demonstrated improvement in numbness, lancinating pain, and allodynia with no changes in vibration, temperature, and pain perception thresholds with TENS therapy.²⁶
- Another study found that HF muscle stimulation was more effective than TENS in improving pain rating scores and peripheral neuropathic symptom reports, but both were effective in decreasing symptoms.³⁴
- There were no risks reported with the use of TENS.

EXPERT OPINION

Low-risk interventions (1) that are consistent with sound clinical practice, (2) that are suggested by an expert in a peer-reviewed publication (journal or book chapter), and (3) for which limited evidence exists. An expert is an individual who has authored articles published in a peer-reviewed journal in the domain of interest.

Important nursing practice includes education and support to preserve patient safety.³⁵⁻³⁸

- Teach patients the signs and symptoms of peripheral neuropathy, and instruct patients to report them to their healthcare providers as soon as they or their families notice them.
- Teach patients strategies for managing personal safety, such as using visual input to compensate for loss of lower-extremity sensation in navigating changing terrain, removing throw rugs, clearing walkways of clutter, using skid-free shower and bathroom mats, or using a cane or walker if gait is unsteady.
- Teach patients the principles of foot care, including inspection of the feet and the importance of wearing properly fitted shoes.
- Teach patients about preventing the risk for ischemic or thermal injury resulting from loss of sensation in extremities, such as lowering water temperature in the home water heater to avoid burns, using a bath thermometer to make sure the temperature of water in the shower or tub is 120°F or below, and inspecting the hands and feet every day for sores or blisters.

- Teach strategies to prevent symptoms of autonomic dysfunction (postural hypotension, constipation, urinary retention), such as dangling the legs prior to arising and consuming a high-fiber diet and adequate fluid intake.

For information on pharmacologic interventions for neuropathic pain, please refer to the ONS Putting Evidence Into Practice pain resources, being published in fall 2007.

Authors: Constance Visovsky, PhD, RN, ACNP, Mary Collins, MSN, RN, OCN®, Connie Hart, BSN, RN, OCN®, Linda Abbott, RN, MSN, AOCN®, CWON, and Julie Aschenbrenner, RN, BSN, OCN®

Oncology Nursing Society
125 Enterprise Drive, Pittsburgh, PA 15275-1214
412-859-6100

Definitions of the interventions and full citations: www.ons.org/outcomes
Literature search completed through December 2006

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