ASCO special articles

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update

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abstract

PURPOSE To update the ASCO guideline on the recommended prevention and treatment approaches in the management of chemotherapy-induced peripheral neuropathy (CIPN) in adult cancer survivors.

METHODS An Expert Panel conducted targeted systematic literature reviews to identify new studies.

RESULTS The search strategy identified 257 new references, which led to a full-text review of 87 manuscripts. A total of 3 systematic reviews, 2 with meta-analyses, and 28 primary trials for prevention of CIPN in addition to 14 primary trials related to treatment of established CIPN, are included in this update.

RECOMMENDATIONS The identified data reconfirmed that no agents are recommended for the prevention of CIPN. The use of acetyl-L-carnitine for the prevention of CIPN in patients with cancer should be discouraged. Furthermore, clinicians should assess the appropriateness of dose delaying, dose reduction, substitutions, or stopping chemotherapy in patients who develop intolerable neuropathy and/or functional impairment. Duloxetine is the only agent that has appropriate evidence to support its use for patients with established painful CIPN. Nonetheless, the amount of benefit from duloxetine is limited.

Additional information is available at www.asco.org/survivorship-guidelines.

J Clin Oncol 38:3325-3348. © 2020 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on May 15, 2020 and published at ascopubs.org/journal/jco on July 14, 2020: DOI https://doi.org/10.1200/JCO.20.01399

Clinical Practice Guidelines Committee approval: May 5, 2020

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INTRODUCTION

Chemotherapy-induced neuropathy is a serious clinical problem caused by a substantial number of cytotoxic drugs, including taxanes, platinums, vinca alkaloids, epothilones, eribulin, and bortezomib; these drugs cause different pathologic insults to neurons. Although there are differences and similarities between the neuropathies caused by these agents, historically, they have not been well defined. Inconsistent measurement methods have often been used to characterize the variations in neuropathy caused by different chemotherapy drugs. However, the same validated neuropathy measurement tools have been recently used in several clinical studies. The data arising from these studies allow for a more detailed comparison of neuropathy clinical manifestations caused by two of the most prominent neurotoxic chemotherapy agents, paclitaxel and oxaliplatin.[1-4]

Both oxaliplatin and paclitaxel cause acute neuropathy. Oxaliplatin-induced acute neuropathy is characterized by cold sensitivity, throat discomfort, discomfort swallowing cold liquids, and muscle cramps. Although some of these symptoms can occur within the time of drug infusion, their severity usually peaks 2 to 3 days after each dose of oxaliplatin. With subsequent treatment cycles, symptom severities double in magnitude over that seen for the first treatment cycle. Oxaliplatin-induced acute neuropathy does not return to baseline between cycles when oxaliplatin is administered once every 2 weeks. There is no good information to delineate how long acute symptoms last after the last dose of oxaliplatin.

Paclitaxel also frequently causes a pain syndrome that occurs in the days following each dose. These symptoms, in the past, had been labeled as being arthralgias or myalgias. However, newer data support that they are a manifestation of an acute neuropathy.[2,5] These acute neuropathy symptoms from paclitaxel present with a similar time pattern as oxaliplatin acute neuropathy symptoms, peaking approximately 2 to 3 days after each dose of paclitaxel. The symptom complex, however, is different than that seen with oxaliplatin, in that it is primarily a pain, classically occurring in a truncal/hip distribution. In comparison

THE BOTTOM LINE

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update

Guideline Question

What are the recommended prevention and treatment approaches in the management of chemotherapy-induced neuropathies in adult cancer survivors?

Target Population

Adult cancer survivors with, or at risk for developing, chemotherapy-induced neuropathies

Target Audience

Health care practitioners who provide care to cancer survivors; patients and their caregivers

Methods

An Expert Panel was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

Updated Recommendations

The following recommendations are evidence based, informed by randomized trials, and guided by clinical experience. The recommendations were developed by a multidisciplinary group of experts.

Prevention of chemotherapy-induced peripheral neuropathy.

1.1 Clinicians should assess the risks and benefits of agents known to cause CIPN among patients with underlying neuropathy and with conditions that predispose to neuropathy such as diabetes and/or a family or personal history of hereditary neuropathy (Type of recommendation: Informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

1.2 Clinicians should not offer, and should discourage use of, acetyl-L-carnitine for the prevention of CIPN in patients with cancer (Type of recommendation: evidence based, harms outweigh benefits; Evidence quality: high; Strength of recommendation: strong).

1.3 Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the prevention of CIPN:

- Acupuncture
- Cryotherapy
- Compression therapy
- Exercise therapy
- Ganglioside-monosialic acid (GM-1)

(Type of recommendation: no recommendation; Evidence quality: low; Strength of recommendation: not applicable).

Note: While preliminary evidence suggests a potential for benefit from these interventions, larger sample–sized definitive studies are needed to confirm efficacy and clarify risks.

1.4 Clinicians should not offer the following agents for the prevention of CIPN to patients with cancer undergoing treatment with neurotoxic agents:

- All-trans retinoic acid
- Amifostine
- Amitriptyline
- Calcium magnesium
- Calmangafodipir
- Cannabinoids
- Carbamazepine
- L-carnosine
- Diethyldithiocarbamate (DDTC)
- Gabapentin/pregabalin
- Glutamate
- Glutathione (GSH) for patients receiving paclitaxel/carboplatin chemotherapy
- Goshajinkigan (GJG)
- Metformin

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THE BOTTOM LINE (CONTINUED)

- Minocycline
- *N*-acetylcysteine
- Nimodipine
- Omega-3 fatty acids
- Org 2766
- Oxcarbazepine
- Recombinant human leukemia inhibitory factor
- Venlafaxine
- Vitamin B
- Vitamin E

(Type of recommendation: evidence based, no benefits; Evidence quality: intermediate; Strength of recommendation: moderate).

Treatment of chemotherapy-induced peripheral neuropathy that develops while patients are receiving neurotoxic chemotherapy.

2.1 Clinicians should assess, and discuss with patients, the appropriateness of dose delaying, dose reduction, or stopping chemotherapy (or substituting with agents that do not cause CIPN) in patients who develop intolerable neuropathy and/or functional nerve impairment (Type of recommendation: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Treatment of chemotherapy-induced peripheral neuropathy for patients who have completed neurotoxic chemotherapy.

3.1 For patients with cancer experiencing painful CIPN, clinicians may offer duloxetine (Type of recommendation: evidence based, benefits equal harms; Evidence quality: intermediate; Strength of recommendation: moderate).

3.2 Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the treatment of CIPN:

- Exercise therapy
- Acupuncture
- Scrambler therapy
- Gabapentin/pregabalin
- Topical gel treatment containing baclofen, amitriptyline HCL, plus/minus ketamine
- Tricyclic antidepressants
- Oral cannabinoids

(Type of recommendation: no recommendation; Evidence quality: low; Strength of recommendation: not applicable).

Note: While recent preliminary evidence suggests a potential for benefit from exercise, acupuncture, and scrambler therapy, larger sample-sized definitive studies are needed to confirm efficacy and clarify risks.

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/survivorship-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

with oxaliplatin-related symptoms, these symptoms tend to resolve more between doses of paclitaxel, and the symptoms are not worsened, on average, in subsequent cycles.

The chronic neuropathies related to these 2 drugs share several similarities. The neuropathy associated with each drug is primarily sensory, as opposed to motor or autonomic. The most common descriptors of this sensory neuropathy are numbness, tingling, and pain. Numbness and tingling appear earlier and are generally more prominent problems than pain. A stocking-glove distribution of symptoms typically begins distally in the fingers and toes and can progress proximally as the condition worsens.

When comparing chronic neuropathy distribution patterns between the 2 drugs, paclitaxel-induced chronic neuropathy symptoms are more prominent in the lower extremities than upper extremities during treatment. In contrast,

oxaliplatin-induced symptoms experienced during treatment are more severe in the upper extremities than in the lower extremities.

After completion of chemotherapy treatments, paclitaxel neuropathy, on average, improves over the ensuing several months. In contrast, oxaliplatin-induced neuropathy, on average, worsens for 2-3 months after cessation of therapy (labeled as coasting phenomenon); after approximately 3 months, neuropathy tends to improve.[3] Neuropathy in the hands improves faster than in the feet, so that, months after completion of oxaliplatin, neuropathy is worse in the feet than in the hands. Although neuropathy caused by both drugs tends to improve over time, neuropathy can remain as a substantial debilitating problem in a subset of patients for years.[6,7]

The diagnosis of the more chronic chemotherapy-induced peripheral neuropathy can generally be made by clinical history. If a patient receiving neurotoxic chemotherapy develops new or worsening numbness, tingling, and/or pain in their hands and/or feet, and there is no other good reason for them to have developed these symptoms, then the diagnosis is made. Neurologic physical examination can be abnormal in a patient with chemotherapy-induced peripheral neuropathy. Neurologic tests, such as electromyography (EMG), can be used but are not usually necessary. There are data supporting that nerve conduction studies in asymptomatic patients who are receiving neurotoxic chemotherapy can predict the development or worsening of chemotherapy-induced peripheral neuropathy (CIPN).[8-10] These tests, however, are not routinely used.

Chemotherapy-induced peripheral neuropathy can markedly affect the quality of life (QOL) of patients. In addition, it may be detrimental to their cancer outcomes, as it may limit the amount of chemotherapy that clinicians can give.

The purpose of this guideline update is to systematically review new evidence reported in the literature since the original guideline was published, compare outcomes among trials, and provide updated guidance on the effectiveness of prevention and treatment options for CIPN in adults with a history of cancer.

GUIDELINE QUESTIONS

This clinical practice guideline addresses 2 overarching clinical questions: What are the recommended (1) prevention and (2) treatment approaches in the management of chemotherapy-induced neuropathies in adult cancer survivors?

METHODS

Guideline Update Development Process

This systematic review-based guideline was developed by a multidisciplinary expert panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met via webinar and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were made available for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. The full guideline was shared with 2 external reviewers. Comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed using a systematic review and informed by expert clinical experience. PubMed was searched for randomized controlled trials (RCTs) and meta-analyses published between January 1, 2013, and August 28, 2019. An updated search was conducted in February 2020. Search terms are provided in the Data Supplement. Randomized trial articles were selected for inclusion in the systematic review of the evidence if they (1) focused on chemotherapy-induced neuropathy, (2) included cancer survivors, and (3) considered neuropathy as an important outcome of the study. Articles were excluded from the systematic review if they (1) were phase I studies, other noncomparative studies, case reports, editorial letters, or newspaper articles; (2) only involved individuals < 18 years of age; (3) were published in a language other than English; (4) included < 10 participants; or (5) focused on radiation therapy–related neuropathy or stem-cell transplantation–related neuropathy.

The updated search was guided by the "signals"[11] approach that is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted routine literature searching and the expertise of ASCO Expert Panel members to help identify potential signals. Before publication, a review of guideline implementability was also conducted. Ratings for the type and strength of the recommendation and the quality of evidence are provided with each recommendation, using standardized criteria that are applied to all ASCO guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline update.

The ASCO Expert Panel and guidelines staff will continue to work with co-chairs in the future to keep abreast of the need

for any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

The review of prevention and treatment of CIPN identified a total of 31 prevention and 14 treatment publications that met eligibility criteria and form the evidentiary basis for the guideline updated recommendations. Characteristics and key results of these publications, by clinical question, are provided in Tables 1 and 2. Studies that were particularly pertinent to the development of the recommendations are discussed in the Literature Review Update and Analysis sections.

Study Quality Assessment

Study quality was formally assessed for the 45 intervention studies identified. Systematic reviews and meta-analyses were assessed for quality using the AMSTAR tool.[12] Design elements such as blinding, allocation concealment, sufficient sample size, intention to treat, and funding sources were assessed for RCTs. AMSTAR scores ranged from 8 to 9 out of a possible 11 points. Overall, the included systematic reviews were conducted in a rigorous fashion; however, many of the primary studies included in these reviews suffered from flaws in study design. Additional RCTs identified and included in this guideline ranged from low to high overall risk of bias. Many of these trials also had flaws in the study design, mainly around blinding; had small sample sizes and/or high attrition rates; and lacked statistical power, thus lowering the confidence in the findings. The included studies were also heterogeneous with respect to patient populations, sample size, methodological quality, treatment duration, and outcome measures. The primary outcomes varied across studies and, in the majority of cases, were not directly comparable because of different outcomes, measurements, and instruments used at different time points. This diversity precluded a quantitative analysis and, as such, only a qualitative review was performed. Refer to the Data Supplement for quality rating scores and the Methodology Manual (http://www.asco.org/guideline-methodology) for definitions of ratings for overall potential risk of bias.

UPDATED RECOMMENDATIONS

CLINICAL QUESTION

What are the recommended prevention and treatment approaches in the management of chemotherapy-induced neuropathies in adult cancer survivors?

Prevention of Chemotherapy-Induced Peripheral Neuropathy

1.1 Clinicians should assess the risks and benefits of agents known to cause CIPN among patients with underlying neuropathy and with conditions that

TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
Acetyl-L-carnitine						
Hershman et al[7]	Double-blind, randomized phase III study	Taxane-based chemotherapy	409	1,000 mg 3 times a day	ALC group had a statistically significantly ($P = .01$) greater worsening of NTX scores of −1.39 points (95% CI, −2.48 to −0.30).	
Campone et al[14]	Double-blind, randomized phase II study	Sagopilone	150	1,000 mg every 3 days	No significant differences between the 2 treatment arms for peripheral neuropathy overall; median duration of neuropathy was similar.	
Alpha-lipoic acid						
Guo et al[17]	Phase III randomized, double-blind, placebo-controlled trial	Cisplatin or oxaliplatin	243	600 mg 3 times a day	No significant differences between the 2 treatment arms for peripheral neuropathy	Only 70 of 243 patients (29%), completed the study
Calcium and magnesium						
Jordan et al[18]	Systematic review and meta-analysis	Oxaliplatin	694 patients from 5 trials	CaMg infusions	Incidence of grade ≥ 2 neuropathy: RR, 0.81; 95% CI, 0.60 to 1.11. Incidence of chronic neurotoxicity for all grades: pooled RR of 0.95 (95% CI, 0.69 to 1.32).	Concluded that CaMg was not beneficial for decreasing oxaliplatin-induced neuropathy
Han et al[21]	Randomized, pilot, double-blind, placebo-controlled, crossover trial	Oxaliplatin	19	1 g of each IV before and after chemotherapy	No acute neuropathy differences between the 2 study arms. No differences in EMG motor nerve hyperexcitability scores between arms.	
Calmangafodipir						
Glimelius et al[22]	Placebo-controlled randomized phase II study	Oxaliplatin	173	Calmangafodipir was given as a 5-minute infusion 10 minutes before oxaliplatin	Calmangafodipir-treated patients (all 3 doses pooled) did not have significantly less physician-graded neurotoxicity (OR, 0.62; 90% CI, 1-sided upper level, 1.15; $P = .16$) but had significantly fewer sensory symptoms in the Leonard scale (cycle 1-8 mean, 1.9 *v* 3.0; $P < .05$ and during follow-up after 3 and 6 months, mean 3.5 *v* 7.3; $P < .01$).	
L-carnosine						
Yehia et al[23]	Randomized controlled pilot trial	Oxaliplatin	65	Arm A, 31 patients received FOLFOX-6 regimen (oxaliplatin, FU, and leucovorin); arm B, 34 patients received FOLFOX-6 regimen and daily oral L-carnosine (500 mg) along the treatment period	Neuropathy grade 2: arm A: 19 patients (61.3%); arm B: 1 patient (3.3%)	

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TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline (continued)

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
Cryotherapy, compression therapy, cryo-compression therapy						
Hanai et al[25]	Prospective, self-controlled clinical trial	Paclitaxel	36	Each patient wore flexible FGs and socks on the dominant hand and foot from 15 minutes before paclitaxel administration to 15 minutes after the infusion was complete (90 minutes in total). FGs were replaced after the first 45 minutes. The nondominant side acted as the untreated control.	Incidence of objective and subjective CIPN signs was clinically and statistically significantly lower on the intervention side than on the control. Hand: OR, 20.00; 95% CI, 3.20 to 828.96; $P < .001$; foot: OR, infinite; 95% CI, 3.32 to infinite; $P < .001$; warm sense: hand: OR, 9.00; 95% CI, 1.25 to 394.48; $P = .02$; foot: OR, 5.00; 95% CI, 1.07 to 46.93; $P = .04$	No withdrawals for toxicity
Beijers et al[26]	Prospective, randomized trial	Paclitaxel, docetaxel, or oxaliplatin	180	Patients were randomly assigned between wearing FGs on both hands during treatment or not wearing FGs.	ITT analyses, EORTC CIPN20 subscales: no statistically significant differences between intervention and control groups. In cryotherapy arm: less tingling in fingers/hands ($P = .005$); less trouble opening a jar ($P = .04$); EORTC QLQ-C30 quality of life better ($P = .03$)	34% discontinued the FGs before end of chemotherapy mainly due to discomfort. The EORTC CIPN20 subscales include data on lower extremities, which were not cooled in this trial.
Ruddy et al[27]	Prospective, randomized pilot, phase II study	Paclitaxel	42	Hands and feet were cooled starting 15 minutes before each paclitaxel dose and continued for 15 minutes after each dose was complete.	No difference in CIPN20 scores between the study arms, but cross-study comparisons suggested benefit from cryotherapy	
McCarthy et al[28]	Prospective, randomized study	Docetaxel	53	Participants acted as their own control, with the frozen gel glove worn on 1 randomly assigned hand starting 15 minutes before infusion and continuing until 15 minutes after completion of treatment.	No significant differences were determined between hand conditions in terms of time to event or in terms of toxicity in gloved and nongloved hands.	60% withdrawal rate due to patient discomfort with the intervention
Bandla et al[31]	Internally controlled pilot trial	Paclitaxel	20	Patients underwent limb hypothermia of 1 leg for a duration of 3 hours with every paclitaxel infusion, with the contralateral limb used as control.	Grade 3 PN occurred in 2 patients (10%), grade 2 in 2 (10%), and grade 1 in 12 (60%). Significant correlation was observed between amount of skin cooling and motor nerve amplitude preservation at 6 months ($P < .0005$). Sensory velocity and amplitude in the cooled limbs were less preserved than in the control limbs, but the difference did not attain statistical significance.	Well tolerated, with no premature termination of cooling due to intolerance.
Kanbayashi et al[34]	Phase II, self-controlled clinical trial	Paclitaxel	38	During chemotherapy, patients wore an FG on one hand and 2 SGs of the same size (ie, 1 size smaller than the size that best fits the hand) on the other hand.	Frequencies of CTCAE grade ≥ 2 was 18.4% in both groups. Frequencies of PNQ grade $\geq$ D peripheral neuropathies was 2.6% in both groups. No difference was identified between FG and SG groups in PNQ sensory neuropathy ($P = .32$-1.0), PNQ motor neuropathy ($P = .51$-1.0), or total FACT-T score ($P = .67$-$.93$) at each evaluation time.	Authors concluded that both approaches appeared to have similar benefits.

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TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline (continued)

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
Tsuyuki et al[33]	Self-controlled clinical trial	Paclitaxel	42	Each patient wore 2 SGs on the dominant hand; both were 1 size smaller than the size that would normally fit the patient's hand. The nondominant hand served as the control (ie, did not wear SGs or anything else).	Compared with the control hands, the SG-protected hands: maintained significantly lower incidences of grade 2 or higher PN over time, despite the increase in nab-PTX treatment cycles ($P < .0001$); significantly decreased the overall occurrence of CTCAE grade ≥ 2 PN from 76.1% to 21.4% for sensory neurotoxicity and from 57.1% to 26.2% for motor neurotoxicity; sensory and motor incidences of grade ≥ 4 PNQ responses were significantly higher (ie, more interference with activities of daily living) for control hands than for SG-protected hands (sensory 38.1% *v* 7.1%; motor 23.8% *v* 2.4%).	During the administration of nab-PTX, 9 patients (21.4%) were permitted to take additional medications, such as goshajinkigan, pregabalin, and/or duloxetine, because PN grade ≥ 2 affected their control hands and/or feet.
Griffiths et al[29]	Randomized, self-controlled clinical trial	Paclitaxel	29	Patients wore a glycerin-containing Elasto-Gel glove and sock over a disposable glove and sock liner maintained at −25 to −30°C in a freezer for 3 hours before application. To maintain the appropriate cold, the study coordinator replaced the glove and sock every 45 to 50 minutes during the treatment of a total duration of 210 minutes.	There was no significant difference in NPSI scores between treated and untreated hands (all $P > .15$) or feet (all $P > .30$) at any assessment point; this remained true even when limiting analysis to the subset of 7 participants who had data for the final post-chemotherapy assessment.	Ten (34%) participants could not tolerate the cryotherapy, and 6 (21%) declined further participation at some point during the trial. Only 7 participants (24%) were available for the final post-chemotherapy QST and questionnaires.
Exercise						
Zimmer et al[36]	Randomized controlled trial	Various regimens for patients with metastatic colorectal cancer	30	Intervention included 8-week supervised exercise program, including endurance, resistance, and balance training (2×/wk for 60 minutes) *v* control group received written standard recommendations for physical fitness.	Neuropathic symptoms remained stable in the intervention group over time, while CIPN significantly worsened in the control group from baseline to 8 weeks and from baseline to 4 weeks postintervention completion follow-up. The intervention group also significantly improved in strength and balance function compared with the controls. Changes in CIPN correlated with changes in balance.	
Kleckner et al[35]	Randomized controlled trial	Taxane-, platinum-, or vinca alkaloid–based chemotherapy	355	Intervention included chemotherapy plus EXCAP, a standardized, individualized, moderate-intensity, home-based, 6-week progressive walking and resistance exercise program.	Exercise significantly reduced CIPN symptoms of: hot/coldness in hands/feet (−0.46 units; $P = .045$); numbness and tingling (−0.42 units; $P = .061$) was not statistically significantly reduced compared with the control.	This trial was developed to study fatigue, but CIPN data were also collected.

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TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline (continued)

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
GM-1						
Zhu et al[39]	Randomized trial	Oxaliplatin	120	100 mg once daily IV	Less neuropathy in the investigational treatment arm, compared with the control group.	Clinician-reported neuropathy, not patient-reported. Lack of a placebo arm introduces a potential bias
Su et al[38]	Randomized trial	Taxanes	206	80 mg, day −1 to day 2	Functional Assessment of Cancer Treatment Neurotoxicity subscale GM-1: 43.3 (95% CI, 43.1 to 43.5). Placebo: 34.3 (95% CI, 33.8 to 34.9); mean difference, 8.96 (95% CI, 8.4 to 9.5; $P < .001$). Grade ≥ 1 peripheral neurotoxicity in CTCAE v4: GM-1: 14.3%; placebo: 100.0%; $P < .001$. Incidence of grade ≥ 1 neurotoxicity by ECOG. Sensory neuropathy: GM1: 26.4% *v* placebo: 97.8%; $P < .001$. Motor neuropathy: GM-1: 20.9%; placebo: 81.5%; $P < .001$	Peculiar total reversal of CIPN 3 months after taxane completion, which has not been observed in other trials.
Goshajinkigan						
Kuriyama et al[41]	Systematic review and meta-analysis	—	397, from 5 trials	—	Reduced incidence of CIPN grade ≥ 1: RR, 0.43; 95% CI, 0.27 to 0.66. Reduced incidence of CIPN grade ≥ 2: not statistically significant. Reduced incidence of CIPN grade 3: RR, 0.42; 95% CI, 0.25 to 0.71.	Authors concluded that, given the low quality and insufficient amount of the evidence, use of goshajinkigan as standard of care is not currently recommended.
Metformin						
El-Fatatry et al[42]	Randomized controlled trial	Oxaliplatin	40	Patients in the metformin group received the same chemotherapeutic regimen as the control group in addition to metformin 500 mg 3 times daily after meals throughout the 12 cycles of chemotherapy.	NCI-CTCAE peripheral neuropathy grading: at the end of 12th cycle, there were significantly fewer patients with grade 2-3 neuropathy in metformin arm compared with control arm (60% *v* 95%; $P = .009$). The Ntx-12 questionnaire: at the end of the 6th cycle and on to 12th cycle, metformin group showed significantly higher mean scores than control group (37.8 *v* 34.5; $P = .0001$ and 24.0 *v* 19.2; $P < .0001$, respectively). The BPI-SF "worst pain": At the end of 11th and 12th cycles, metformin group showed significantly lower mean pain scores than control group (6.4 *v* 6.9; $P = .01$ and 6.7 *v* 7.3; $P = .001$, respectively).	

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TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline (continued)

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
Pregabalin						
de Andrade et al[44]	Randomized, double-blind, placebo-controlled trial	Oxaliplatin	143	3 days before and 3 days after each oxaliplatin infusion.	Pain intensity: pregabalin: 1.03 (95% CI, 0.79 to 1.26); placebo: 0.85 (95% CI, 0.64 to 1.06). Not significant. Scores from the BPI, MPQ, DN-4, NPSI, and NCS and side-effect profiles and incidence of death did not differ between groups. QOL score: pregabalin group: 79.4 ± 20.6; placebo, 76.9 ± 23.1	
Shinde et al[43]	Pilot randomized, double-blind, placebo-controlled trial	Paclitaxel	46	75 mg/d	Not enough positive evidence to support a phase III trial.	
Gabapentin						
Aghili et al[45]	Randomized, placebo-controlled trial	Paclitaxel	40	300 mg 3 times a day	Difference in neuropathy grading between the gabapentin and control group were statistically significantly in favor of gabapentin in each treatment cycle ($P <$ .004). Change in baseline nerve conduction velocity after 4 cycles of paclitaxel was statistically significantly lower in the gabapentin group compared with placebo (sural nerve: 17.7% ± 37.2% *v* 61.0% ± 48.0%; $P = .004$; peroneal nerve: 21.9% ± 41.5% *v* 62.5% ± 53.5%; $P = .016$).	
Venlafaxine						
Zimmerman et al[47]	Pilot randomized, double-blind, placebo-controlled trial	Oxaliplatin	50	37.5 mg twice a day	Not enough positive evidence to support a phase III trial.	
Vitamin B						
Schloss et al[49]	Pilot, randomized, placebo-controlled trial	Oxaliplatin or vincristine	47	1 capsule, twice a day, of B vitamin complex, which included 50 mg of thiamine, 20 mg of riboflavin, 100 mg of niacin, 163.5 mg of pantothenic acid, 30 mg of pyridoxine, 500 μg of folate, 500 μg of cyanocobalamin, 500 μg of biotin, 100 mg of choline, and 500 μg of inositol.	TNS demonstrated that the B vitamin group did not significantly reduce the incidence of CIPN compared with placebo ($P = .73$). Statistical significance was achieved for patient perceived sensory peripheral neuropathy (12 weeks, $P = .03$; 24 weeks, $P = .005$; 36 weeks, $P = .021$). The risk estimate for the PNQ was also statistically significant (OR, 5.78; 95% CI, 1.63 to 20.5). EORTC QOL, total pain score, and pain interference showed no significance ($P = .46$, $P = .9$, $P = .37$, respectively).	

(continued on following page)

TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline (continued)

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
Vitamin E						
Huang et al[50]	Systematic review and meta-analysis	Platinum-based therapy, paclitaxel-based therapy, and various other chemotherapeutic agents	353 from 6 studies	300 mg daily (1 study); 300 mg twice daily (3 studies); 400 mg daily (1 study)	Incidence of CIPN: RR, 0.55; 95% CI, 0.29 to 1.05; $P = .07$). RR in high-quality trials with low bias risk, 1.03; 95% CI, 0.59 to 1.80; $P = .92$. Subgroup analysis of cisplatin-related neurotoxicity: RR, 0.31; 95% CI, 0.17 to 0.58; $P = .0002$.	Four of the 6 included studies assessed the safety of vitamin E during chemotherapy and no adverse events were observed
Salehi et al[51]	Prospective, randomized controlled study	Oxaliplatin	65	400 mg daily	Mean peripheral neuropathy score changes (mean difference after to before) after sixth course of the oxaliplatin base regimen: vitamin E group: 6.37 ± 2.85; control group, 6.57 ± 2.94; $P = .78$).	
Acupuncture						
Greenlee et al[13]	Randomized sham-controlled trial	Taxanes	63	Selected acupuncture points were attached to 2 leads connected to an electro-stimulator that generated 2 Hz of mixed pulsatile intervals for a total of 30 minutes. Needles not attached to the electro-stimulator were manipulated manually to elicit de qi once during the treatment.	Week 12, increase in mean BPI-SF worst pain score: EA: 2.6; sham EA: 2.8; $P = .86$. Week 16, mean BPI-SF worst pain score: EA: 3.4; sham EA: 1.7; $P = .03$. The increase in BPI-SF worst pain score was 1.62 points higher in the EA group than in the sham EA group at week 16 ($P = .04$).	
Minocycline						
Wang et al[84]	Phase II randomized clinical trial	Oxaliplatin	66	Intervention included 100 mg twice daily minocycline	There was no observed significant symptom reduction on numbness/tingling in either arm, nor was there a difference in levels of serum proinflammatory or antiinflammatory markers between arms.	No grade 3 adverse events were observed
Pachman et al[85]	Randomized pilot study	Paclitaxel	47	Intervention included minocycline 200 mg on day 1 followed by 100 mg twice daily	There were no remarkable differences noted between the minocycline and placebo groups for the overall sensory neuropathy score of the EORTC QLQ-CIPN20 or its individual components, which evaluate tingling, numbness and shooting/burning pain in hands and feet. Patients taking minocycline had a reduction in the daily average pain score attributed to P-APS ($P = .02$).	

Abbreviations: ALC, acetyl-L-carnitine; BPI-SF, Brief Pain Inventory–Short Form; CIPN, chemotherapy-induced peripheral neuropathy; CTCAE, Common Terminology Criteria for Adverse Events; DN-4, Douleur Neuropathique 4 Questions; EA, electro-acupuncture; EMG, electromyography; EORTC, European Organization for Research and Treatment of Cancer; EXCAP, Exercise for Cancer Patients; FACT-T, Functional Assessment of Cancer Therapy-Taxane; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FG, frozen glove; FU, fluorouracil; GM-1, ganglioside-monosialic acid; ITT, intention to treat; IV, intravenous; MPQ, McGill Pain Questionnaire; nab-TPX, nanoparticle albumin-bound paclitaxel; NCI, National Cancer Institute; NCS, nerve conduction studies; NPSI, Neuropathic Pain Symptom Inventory; NTX, neurotoxicity; OR, odds ratio; P-APS, paclitaxel-associated acute pain syndrome; PN, peripheral neuropathy; PNQ, Patient Neurotoxicity Questionnaire; QLQ-C30, Quality of Life Questionnaire-Core 30; QOL, quality of life; QST, quantitative sensory testing; RR, relative risk; SG, surgical glove; TNS, Total Neuropathy Score.

predispose to neuropathy such as diabetes and/or a family or personal history of hereditary peripheral neuropathy (Type of recommendation: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

1.2 Clinicians should not offer, and should discourage use of, acetyl-L-carnitine for the prevention of CIPN in patients with cancer (Type of recommendation: evidence based, harms outweigh benefits; Evidence quality: high; Strength of recommendation: strong).

1.3 Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the prevention of CIPN:

- Acupuncture
- Cryotherapy
- Compression therapy
- Exercise therapy
- Ganglioside-monosialic acid (GM-1)

(Type of recommendation: no recommendation; Evidence quality: low; Strength of recommendation: not applicable).

Note: While preliminary evidence suggests a potential for benefit from these interventions, larger sample–sized definitive studies are needed to confirm efficacy and clarify risks.

1.4 Clinicians should not offer the following agents for the prevention of CIPN to patients with cancer undergoing treatment with neurotoxic agents:

- All-trans retinoic acid
- Amifostine
- Amitriptyline
- Calcium magnesium
- Calmangafodipir
- Cannabinoids
- Carbamazepine
- L-carnosine
- Diethyldithiocarbamate (DDTC)
- Gabapentin/pregabalin
- Glutamate
- Glutathione (GSH) for patients receiving paclitaxel/carboplatin chemotherapy
- Goshajinkigan (GJG)
- Metformin
- Minocycline
- *N*-acetylcysteine
- Nimodipine
- Omega-3 fatty acids
- Org 2766
- Oxcarbazepine
- Recombinant human leukemia inhibitory factor
- Venlafaxine
- Vitamin B
- Vitamin E

(Type of recommendation: evidence based, no benefits; Evidence quality: intermediate; Strength of recommendation: moderate).

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Acupuncture. One small randomized, sham-controlled trial of weekly electro-acupuncture for the prevention of taxane-induced peripheral neuropathy in 63 patients did not show any differences in neuropathy between groups.[13] In this trial, the electro-acupuncture arm actually had a slower recovery of neuropathy than was seen in the sham group, after chemotherapy was stopped.

Acetyl-L-carnitine. Two trials evaluating acetyl-L-carnitine were identified. Campone et al[14] reported data on the use of acetyl-L-carnitine for preventing sagopilone-induced neuropathy in 150 patients randomly assigned to receive acetyl-L-carnitine or placebo. There were no significant differences between the 2 treatment arms for peripheral neuropathy overall, and the median duration of neuropathy was similar.[14] These data are consistent with older data from a previously reported trial in patients receiving paclitaxel, where neuropathy was actually worse in the patients who received acetyl-L-carnitine.[15,16] In a recent long-term follow-up analysis[7] of that trial, 24 weeks of acetyl-L-carnitine therapy resulted in statistically significantly worse CIPN ($P = .01$) over 2 years, as measured by the Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-Ntx) Questionnaire.

Alpha-lipoic acid. One randomized, double-blinded clinical trial that evaluated oral alpha-lipoic acid (ALA) for the prevention of platinum-induced peripheral neuropathy was identified. Patients received 600 mg ALA acid 3 times daily for 24 weeks while receiving chemotherapy. This trial enrolled 243 patients, but only 70 of them (29%) completed the trial. The study authors reported that the high dropout rate may have been related, in part, to the requirement that patients take the drug 3 times per day. Data indicated that neuropathy scores increased significantly from baseline for both groups at 24 weeks ($P < .001$ for each group), with no statistically significant ameliorating effect from ALA in the treatment arm being observed from the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) tool, from pain scores, or from functional test scores. The study results suggest that ALA is not tolerated well and does not prevent neuropathy.[17]

Calcium and magnesium. One systematic review and 1 pilot trial not included in the systematic review evaluating the utility of intravenous calcium and magnesium were identified. The systemic review, which included 694 patients from 5 trials published between 2010 and 2014, confirmed that there was no beneficial effect in terms of the incidence of grade ≥ 2 neuropathy (relative risk [RR], 0.81; 95% CI, 0.60 to 1.11) or chronic neurotoxicity (RR, 0.95; 95% CI, 0.69 to 1.32) from CaMg infusions for the prevention of oxaliplatin-induced peripheral neuropathy.[18] Two older pooled analyses identified from Xu et al[19] and Wen et al[20], which did not come to the same conclusion, should be

TABLE 2. Randomized Controlled Trials for the Treatment of Established CIPN

Investigational Agent/ Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Neuropathy Outcomes	Methods	Comments
Duloxetine and pregabalin						
Farshchian et al[48]	Randomized clinical trial of duloxetine *v* venlafaxine	Various	156	Grades of neuropathy outcomes decreased significantly in venlafaxine and duloxetine groups. Reduction was more considerable in duloxetine group compared with venlafaxine group ($P < .05$).	Patient-reported outcomes and clinical neurologic assessments	
Hirayama et al[58]	Open-label, randomized, crossover study	Various	34	Significant decreased VAS score in duloxetine pain ($P = .04$), numbness ($P = .03$). AEs: no AEs grade > 2 by CTCAE	Patient-reported outcome	Vitamin E was used in the control arm. Crossover data, after a wash-out period, also supported duloxetine benefit.
Salehifar et al[59]	Randomized clinical trial of duloxetine *v* pregabalin	Taxanes	82	Both arms showed statistically significantly decreased CIPN from baseline, and pregabalin was reported to be significantly better than duloxetine.	Patient-reported outcomes and CTCAE evaluations.	Most patients were started on this therapy while they were receiving chemotherapy. Confirmation of these results needed, given other results of other reported gabapentinoid trials.
Topical amitriptyline/ketamine						
Gewandter et al64	Phase III randomized, double-blind, placebo-controlled trial	Various	462	No observed benefit from treatment.	Patient-reported outcome	
Oral mucosal cannabinoid extract						
Lynch et al[63]	Randomized, placebo-controlled crossover pilot study	Various	16	No statistically significant difference between the treatment and the placebo groups on the NRS-PI.	11-point numerical rating scale, patient-reported	Low power
Scrambler therapy						
Loprinzi et al[61]	Randomized phase II pilot trial	Variety	46	Baseline pain, tingling and numbness scores: compared with TENS-treated patients, twice as many scrambler-treated patients had ≥ 50% documented improvement during the 2 treatments. Patients in the scrambler group were more likely than those in the TENS group to recommend their treatment to other patients during both the 2-week treatment period and the 8-week follow-up period ($P < .0001$).	Patient-reported outcomes	Minimal toxicity was observed.
Smith et al[60]	Randomized sham-controlled phase II trial	Variety	46	Average pain, the BPI, and EORTC CIPN-20: no significant differences between the sham and the "real" ST group at day 10, 28, 60, or 90. There was improvement in the sensory subscale of the CIPN-20 at 2 months in the "real" group ($P = .14$).	Patient-reported outcomes	
Acupuncture						
Lu et al[54]	Randomized controlled trial	Taxanes	40	At 8 weeks: PNQ sensory scores: IA, -1.0 ± 0.9; wait-list control group (control): -0.3 ± 0.6; $P = .01$. FACT-NTX summary score: IA, 8.7 ± 8.9; control, 1.2 ± 5.4, $P = .002$; BPI-SF pain severity score: IA: -1.1 ± 1.7; control: 0.3 ± 1.5; $P = .03$	Patient-reported outcomes	No serious adverse effects were observed.
Molassiotis et al[53]	Randomized controlled trial	Variety	87	At 8 weeks: statistically significant differences detected in pain (primary outcome), the clinical neurologic assessment, QOL domains, and symptom distress (all $P < .05$). Fourteen weeks: improvements in pain interference, neurotoxicity-related symptoms, and functional aspects of quality of life were sustained ($P < .05$). Twenty weeks: improvements in physical and functional well-being sustained ($P < .05$).	Patient-reported outcomes and clinical neurologic assessments	

(continued on following page)

TABLE 2. Randomized Controlled Trials for the Treatment of Established CIPN (continued)

Investigational Agent/ Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Neuropathy Outcomes	Methods	Comments
D'Alessandro et al[55]	Randomized controlled pilot trial	NR	33	EORTC QLQ-C30: statistical differences in physical ($P = .03$) and function ($P = .04$) domains. NCI CTCAE Scale and neuropathy sensory symptoms pre- *v* post-treatment: statistically significantly better results in acupuncture group ($P = .01$) *v* control group, which showed no statistically significant differences after 5 weeks ($P = .11$).	Patient-reported outcomes and clinical neurologic assessments	Intervention included 10 sessions of acupuncture, 2 times per week
Han et al[57] (acupuncture plus methylcobalamin)	Randomized controlled trial		98	VAS pain scores: Met + Acu: decreased in 85.7% of patients; control: decreased in 77.6% of patients. VAS pain scores in the Met + Acu group decreased more significantly compared with the control group ($P < .01$). QOL FACT/GOG-Ntx: significant symptom improvement in Met + Acu group ($P < .001$) after therapy, but not in control group ($P > .05$), and the improvement was more significant in the Met + Acu group ($P < .05$). Nerve conduction velocity: after treatments, there was no significant difference in MCV improvement in the Met + Acu group compared with the control group ($P > .05$).	Patient-reported outcomes and clinical neurologic assessments	
Rostock et al[56] (electro-acupuncture)	Randomized controlled trial	Taxanes, platinum derivatives, or vinca alkaloids	60	CIPN perceived symptom severity on a 10-point numeric rating scale: compared with placebo (1.3 ± 1.3) electro-acupuncture showed worse effects (0.8 ± 1.2), resulting in a group difference of −0.3 (CI, −1.4 to 0.8; $P = .705$). No significant differences in sensory nerve conduction studies or quality of life (EORTC QLQ-C30) were found.	Patient-reported outcomes	Study was stopped early at interim analysis as no relevant superiority of electro-acupuncture was detected ($P\alpha_0 > 0.6$).
Exercise						
Kneis et al[86]	Randomized controlled trial	NR	50	At 12 weeks: ITT (n = 41) did not reveal a significant group for sway path in semi-tandem stance after intervention (primary end point). Per-protocol analysis of 37 patients with training compliance ≥ 70%: intervention group reduced their sway path during semi-tandem stance, improved the duration standing on 1 leg on instable surface and reported decreased motor symptoms on CIPN20 motor score.	Patient-reported outcomes	Intervention included endurance plus balance training *v* only endurance training in the control group (both groups did so twice weekly over 12 weeks). Neuropathy measures were not the primary outcome.
Dhawan et al[52]	Randomized controlled trial	Paclitaxel and carboplatin	45	At 10 weeks: significant reduction in neuropathic pain scores ($P < .0001$) and improvement in Functional QOL ($P = .0002$), Symptom QOL ($P = .0003$), Global Health Status QOL ($P = .004$) scores were observed after intervention in the exercise group compared with the usual-care group.	Patient-reported outcomes and clinical neurologic assessments	Intervention included home-based muscle strengthening and balancing exercise for 10 weeks

Abbreviations: AE, adverse effect; BPI, Brief Pain Inventory; CIPN, chemotherapy-induced peripheral neuropathy; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organization for Research and Treatment of Cancer; FACT-NTX, Functional Assessment of Cancer Therapy-Neurotoxicity; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; IA, immediate acupuncture; ITT, intention to treat; MCV, motor conduction velocities; Met + Acu, methylcobalamin plus acupuncture; NCI, National Cancer Institute; NR, not reported; NRS-PI, Numerical Rating Scale-Pain Intensity; PNQ, Patient Neurotoxicity Questionnaire; QOL, quality of life; QLQ-C30, Quality of Life Questionnaire-Core 30; ST, scrambler therapy; TENS, transcutaneous electrical nerve stimulation; VAS, visual analogue scale.

TABLE 3. Summary of Recommendations

Interventions	Strength of Recommendation	Strength of the Evidence	Benefits	Harms[a]
Prevention				
Acetylcysteine	Moderate against	Intermediate	Low	Low
Acetyl-L-carnitine	Strong against	High	No evidence of efficacy	High
Acupuncture	No recommendation	Low	Low	Moderate
Amifostine	Moderate against	Intermediate	Low	Moderate
Amitriptyline	Moderate against	Intermediate	No evidence of efficacy	Moderate
Calcium and magnesium	Moderate against	Intermediate	Low	Low
Cannabinoids	Moderate against	Intermediate		
Calmangafodipir	Moderate against	Intermediate	Low	Low
Carbamazepine/oxcarbazepine	Moderate against	Intermediate	Low	Low
L-carnosine	Moderate against	Intermediate	Low	Low
Compression therapy	No recommendation	Low	Low	Low
Cryotherapy	No recommendation	Low	Low	Moderate
DDTC	Moderate against	Intermediate	No evidence of efficacy	High
Exercise	No recommendation	Low	Low	Low
Gabapentin/pregabalin	Moderate against	Intermediate	Low	Low
GM-1	No recommendation	Low	Low	Low
Glutamate/glutamine	Moderate against	Intermediate	Low	Low
GSH	Moderate against	Intermediate	Low	Low
GJG–Kampo medicine	Moderate against	Intermediate	Low	Low
Metformin	Moderate against	Intermediate	Low	Low
Minocycline	Moderate against	Intermediate	Low	Low
Nimodipine	Moderate against	Intermediate	No evidence of efficacy	Moderate
Omega 3	Moderate against	Intermediate	Low	Low
Org 2766	Moderate against	Intermediate	Low	Low
Retinoic acid	Moderate against	Intermediate	Low	Moderate
rhuLIF	Moderate against	Intermediate	No evidence of efficacy	Low
Venlafaxine	Moderate against	Intermediate	Moderate	Moderate
Vitamin B	Moderate against	Intermediate	Low	Low
Vitamin E	Moderate against	Intermediate	Low	Low
Treatment				
Acupuncture	No recommendation	Low	Low	Low
Duloxetine	Moderate for	Intermediate	Moderate	Low
Exercise	No recommendation	Low	Low	Low
Gabapentin/pregabalin	No recommendation	Low	Low	Low
BAK	No recommendation	Low	Low	Low
Oral cannabinoids	No recommendation	Low	Low	Low
Tricyclic antidepressants	No recommendation	Low	Low	Low
Scrambler therapy	No recommendation	Low	Low	Low

Abbreviations: BAK, topical amitriptyline, ketamine, ± baclofen; DDTC, diethyldithiocarbamate; GJG, goshajinkigan; GM-1, ganglioside-monosialic acid; GSH, glutathione.

[a]Harms are based only on the results of the specific clinical trials in the previous tables and not on any other evaluations of the safety of these treatments.

discounted, as they did not include data from the largest and most recent definitive trial.

A small randomized, placebo-controlled, crossover trial of calcium/magnesium for prevention of oxaliplatin-induced acute neuropathy involved 20 patients and evaluated EMG motor nerve hyperexcitability scores.[21] The authors reported that there were no differences between those who received calcium and magnesium versus placebo in EMG outcomes (mean EMG score Ca/Mg, 6.5; standard deviation [SD], 4.31; and mean placebo score, 6.2; SD, 4.34) or for patient-reported acute neurotoxicity symptoms.[21]

Calmangafodipir. Calmangafodipir was studied in a placebo-controlled 3-arm phase II trial in patients receiving oxaliplatin-based chemotherapy.[22] This trial provided promising enough data to initiate 2 phase III, placebo-controlled clinical trials (ClinicalTrials.gov identifiers: NCT04034355 and NCT04034355), with results forthcoming.

L-Carnosine. A 61-patient randomized trial evaluated a nutraceutical product, L-carnosine, as an agent to try to decrease oxaliplatin-induced neuropathy.[23] Although the study reported remarkably positive results for the study agent over the control arm, there was no placebo used in this trial and it was not double-blinded. Clinicians judged neuropathy severity, as opposed to using patient-reported outcomes. Thus, additional data are necessary to understand the potential utility of this agent.

Cryotherapy/compression therapy/cryo-compression therapy. The first publication suggesting that cryotherapy was helpful for decreasing taxane-induced neuropathy came from Danish investigators, who noted that patients who received distal-extremity cryotherapy for decreasing onycholysis appeared to have reduced amounts of docetaxel-induced neuropathy by approximately 50%.[24] Five trials evaluating cryotherapy were identified. One prospective, self-controlled trial in 36 patients with breast cancer treated weekly with paclitaxel, who wore frozen gloves (FGs) and socks on the dominant side for 90 minutes but not the other side, reported that the development of subjective CIPN symptoms was clinically and statistically significantly delayed during the course of the paclitaxel treatment; the occurrence of subjective CIPN at a cumulative dose of 960 mg/m^2 was reported to be almost completely prevented (severe CIPN; hand: 2.8% *v* 41.7%; odds ratio [OR], infinite; 95% CI, 3.32 to infinite; $P < .001$; foot: 2.8% *v* 36.1%; OR, infinite; 95% CI, 2.78 to infinite; $P < .001$), and the CIPN incidence, as assessed by other objective modalities, was lower on the intervention side.[25] In a larger unblinded RCT, 180 patients started treatment with oxaliplatin, docetaxel, or paclitaxel and were randomly assigned to FGs on both hands during treatment or to usual care.[26] Self-reported CIPN and QOL were measured. Overall neuropathy scores, the primary outcome measure, were not significantly different between the groups, in part because the feet were not treated, and neuropathy in lower extremities is oftentimes more problematic than it is in upper extremities. This study's results did support that FGs reduced neuropathy symptoms in patients' hands and improved some QOL measures. A recently published randomized phase II trial, involving 42 patients, compared cryotherapy (performed with ice packs on hands and feet) to an untreated control group who was not treated with cryotherapy.[27] The area under the curve of the CIPN20 sensory scores over 12 weeks of paclitaxel was not found to differ between the study arms (mean difference, 3.45; 95% CI, −3.13 to 10.02; $P = .26$). However, when the cryotherapy arm was compared with a control arm made up of controls combined from 3 previous trials, the cryotherapy arm had less neuropathy (Wilcoxon rank-sum $P = .01$). The authors of this study reported that the data supported phase III trial testing of this approach.

In a trial that evaluated a unilateral FG in 53 patients receiving docetaxel, 60% of the patients stopped the cryotherapy, and there were no differences between the hands that were randomly assigned to receive it versus not.[28] Likewise, another study described similarly high drop-out rates and did not report positive findings.[29]

One trial evaluated continuous-flow limb hypothermia as a neuroprotective strategy in 20 patients receiving paclitaxel chemotherapy compared with usual care. Patients who received continuous limb hypothermia had less self-reported paclitaxel-induced neuropathy symptoms and had better nerve conduction studies.[30] The same group of researchers also conducted a subsequent proof-of-concept study in patients with cancer receiving taxane chemotherapy.[31] In this study, both cryotherapy and compression therapy (ie, cryo-compression therapy) were given to all 4 limbs in 13 subjects with each dose of paclitaxel. An analysis of nerve conduction studies with cryo-compression, administered at 16°C and a cyclic pressure of 5-15 mm Hg, illustrated preservation of motor amplitudes compared with baseline.[32] In a cross-study comparison with their previous group of patients who had been treated with cryotherapy alone, patients appeared to do better with the combination therapy.[32]

One trial evaluated compression therapy using a tight surgical glove during taxane chemotherapy infusion.[33] The intervention hand side was randomized within 43 patients. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 sensory neuropathies were reported in 21% of the hands that wore the gloves versus 76% of hands that were not gloved.

A recently published small trial (38 patients) compared cryotherapy to compression therapy. This trial had patients use cryotherapy on one hand and compression therapy on the other and reported that similar results were seen with each approach.[34] Additional randomized trials investigating cryotherapy and cryo-compression are ongoing.

Exercise. Three RCTs that evaluated various exercise interventions for the prevention of CIPN were identified. In

a large trial of patients with cancer receiving taxane-, platinum-, or vinca alkaloid–based chemotherapy,[35] 355 patients were randomly assigned to chemotherapy or chemotherapy plus Exercise for Cancer Patients (EXCAP), a standardized, individualized, moderate-intensity, home-based, 6-week progressive walking and resistance exercise program. This unblinded trial was developed to evaluate the effectiveness of exercise on fatigue. As a secondary analysis, data regarding CIPN were also collected; these results supported that, compared with the control, exercise significantly reduced CIPN symptoms of hot/coldness in hands/feet ($P = .045$) and numbness and tingling, although the latter was not statistically significantly reduced compared with the control arm ($P = .06$). The intervention group still developed neuropathy, but less than the control group—a difference of approximately half a point on a 0-10 scale. On the basis of these findings and other preliminary supportive evidence,[36,37] the NCI has recently approved a concept for a randomized cooperative oncology group trial to prospectively address the utility of exercise in this setting.

GM-1. GM-1 is a monosialo-glycosphingolipid that performs an important function in the processes of neurogenesis, nerve development and differentiation, cell recognition, and signal transduction.[38] Two randomized trials investigating GM-1 for CIPN prevention were identified. In the first trial, Zhu et al[39] reported on 120 patients with GI cancers who were treated with oxaliplatin-based chemotherapy randomly assigned to receive intravenous ganglioside-monosialic acid or to a control group that received no neuroprotective agents. Although the grade of neurotoxicity in the experimental group was significantly lower than in the control group ($P < .05$, Mann-Whitney U test), the lack of placebo control and the lack of patient-reported outcome data decrease the confidence of this finding.[39]

The second trial was a placebo-controlled, double-blinded study of intravenous GM-1, given to prevent taxane-induced CIPN in 183 patients with early-stage breast cancer. The study reported that treatment with GM-1 resulted in a statistically significant reduction in the severity and incidence of CIPN after 4 cycles of taxane-containing chemotherapy ($P < .001$).[38] A peculiar aspect of this trial is that the neuropathy appeared to be totally reversed in the placebo arm 3 months after chemotherapy completion, which is quite unusual in Western populations.[40] Despite this very positive report, a confirmatory trial is needed.

Goshajinkigan. Our systematic review found a meta-analysis that pooled data from 5 trials and included 397 patients. The review reported that goshajinkigan was not associated with a reduced incidence of CIPN when assessed with the CTCAE (RR, 0.99; 95% CI, 0.53 to 1.85 for CIPN ≥ grade 2).[41] Our systemic review did not find additional studies with goshajinkigan that were not included in this meta-analysis.

Metformin. One small randomized study (N = 40) that evaluated metformin as a means of preventing oxaliplatin-induced neuropathy compared with a control group was identified.[42] The authors reported that, at the end of the 12th FOLFOX-4 (fluorouracil, leucovorin, and oxaliplatin) regimen cycle, grade 2-3 neuropathy was lower in the metformin arm compared with the control arm (60% *v* 95%; $P = .009$), and the metformin arm had better NTX-12 scores (24.0 *v* 19.2; $P < .001$). Given the small sample size, more confirmatory studies are needed before recommending this approach for oxaliplatin-induced neuropathy.

Gabapentin/pregabalin. Two randomized placebo-controlled trials investigating pregabalin were identified. On the basis of pilot study information, which suggested that gabapentinoids could decrease paclitaxel-associated acute pain and chronic neuropathy, investigators developed a phase II placebo-controlled clinical trial (N = 46) to look at pregabalin for preventing these neuropathic problems. The results did not support that pregabalin was helpful for preventing the paclitaxel-associated acute pain syndrome or paclitaxel-induced peripheral neuropathy.[43]

In another double-blind, placebo-controlled trial, 143 pain-free, chemotherapy-naive patients with colorectal cancer receiving at least 1 cycle of modified FLOX (ie, fluorouracil, leucovorin, and oxaliplatin) were randomly assigned to receive either pregabalin or placebo for 3 days before and 3 days after each oxaliplatin infusion. After following patients for up to 6 months, the authors reported that preemptive use of pregabalin during oxaliplatin infusions did not decrease the incidence of chronic pain related to oxaliplatin, measured by pain intensity and QOL scales.[44] An additional randomized, double-blinded, placebo-controlled trial of pregabalin involving 64 patients who were receiving oxaliplatin chemotherapy was terminated early, as an interim analysis found that there were not sufficiently positive data to continue the trial.[15]

A small study (20 patients per arm) evaluating gabapentin 300 mg 3 times a day in a double-blind, randomized trial in patients receiving paclitaxel was identified.[45] Although the authors reported a significant reduction in CIPN, confirmation of this is needed in a subsequent trial.

Venlafaxine. One trial investigating the efficacy of venlafaxine on prevention of CIPN was identified. Pursuant to data from Durand et al[46] discussed in the initial ASCO CIPN guideline, this phase II randomized, placebo-controlled clinical trial was conducted to look at venlafaxine as a drug to decrease neuropathy associated with oxaliplatin.[47] Fifty patients were randomly assigned to venlafaxine or placebo, given continuously with initiation of the first or second cycle of oxaliplatin. The trial results did not support the use of venlafaxine in this setting, dampening enthusiasm for proceeding with a phase III trial.[47] Notably, the Durand et al[46] study started venlafaxine/placebo after

patients had received some oxaliplatin, in contrast to at oxaliplatin initiation. Given that there are now data that support that venlafaxine may decrease symptoms in patients with established neuropathy (although not as well as duloxetine),[48] it may be that in the Durand et al[46] trial venlafaxine was potentially acting as an agent that treated established neuropathy, as opposed to acting as a prevention agent.

Vitamin B. A 71-patient placebo-controlled 2-arm trial evaluated an oral vitamin B product in patients who were receiving a variety of neurotoxic drugs (taxanes, oxaliplatin, or vincristine).[49] Data were only available for 47 patients and, understandably with this small sample size and the variety of chemotherapy drugs, there was no suggestion that the primary end point was improved in the vitamin B arm.

Vitamin E. One systemic review and meta-analysis plus another trial not included in the meta-analysis were identified. The systematic review and meta-analysis of 6 studies that included 353 patients reported that the administration of vitamin E (at doses that included 300 mg daily, 300 mg twice daily, and 400 mg daily) did not decrease the incidence of CIPN (RR, 0.55; 95% CI, 0.29 to 1.05; $P = .07$.[50] The small study published subsequently to the meta-analysis[51] also concluded that vitamin E did not help to prevent oxaliplatin-induced peripheral neuropathy.

Clinical interpretation regarding efforts to prevent CIPN. The current review did not find studies supporting the recommendation of any neuropathy-preventative agent. Unlike the promising original guideline commentary regarding venlafaxine as a preventative agent, the updated guideline does not recommend it. A negative follow-up study with a similar number of patients, which treated patients for a longer time period and used a more accepted chemotherapy neuropathy patient-reported outcome measurement tool, backs this.[47]

Given the dearth of effective established agents for preventing chemotherapy-induced neuropathy and the limited effective therapy for treating established CIPN, patients/clinicians should weigh the benefits of using neuropathy-inducing agents against the risks of developing long-term, irreversible CIPN.

Although proof of benefit has not been established, available data support that exercise, cryotherapy, compression therapy, and/or cryo-compression therapy may, in part, prevent CIPN symptoms and appear to be reasonably safe, although clinicians and patients should be aware of frostbite risk. Ganglioside-monosialic acid seemed to be effective in preventing taxane-induced peripheral neuropathy in Chinese patients, but this should be confirmed in a large trial in a different ethnic group. Ongoing trials are attempting to better define whether one or more of these methods will safely prevent CIPN.

Treatment of Chemotherapy-Induced Peripheral Neuropathy That Develops While Patients Are Receiving Neurotoxic Chemotherapy

2.1 Clinicians should assess, and discuss with patients, the appropriateness of dose delaying, dose reduction, or stopping chemotherapy (or substituting with agents that do not cause CIPN) in patients who develop intolerable neuropathy and/or functional nerve impairment (Type of recommendation: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Clinical interpretation. Although there are limited clinical trial data available to guide practice when patients develop CIPN during the course of neurotoxic chemotherapy, this is a common clinical practice situation. Scenarios vary from patients who are being treated with curative intent versus palliative-intent chemotherapy for advanced cancer. Clinicians and patients may make different decisions for continuing neurotoxic chemotherapy in patients suffering from significant neuropathy, based on whether the patient is receiving adjuvant chemotherapy that might improve survival probabilities by a percentage point or two, versus a patient receiving adjuvant chemotherapy expected to improve survival probabilities by many percentage points, versus a patient with metastatic disease. In these individual situations, clinicians may determine whether to reasonably use alternative chemotherapy regimens that do not cause neurotoxicity. Clinicians should obtain individual patient perspectives in all these situations.

Treatment of Chemotherapy-Induced Peripheral Neuropathy for Patients Who Have Completed Neurotoxic Chemotherapy

3.1 For patients with cancer experiencing painful CIPN, clinicians may offer duloxetine (Type of recommendation: evidence based, benefits equal harms; Evidence quality: intermediate; Strength of recommendation: moderate).

3.2 Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the treatment of CIPN:

- Exercise therapy
- Acupuncture
- Scrambler therapy
- Gabapentin/pregabalin
- Topical gel treatment containing baclofen, amitriptyline HCL, plus/minus ketamine
- Tricyclic antidepressants
- Oral cannabinoids

(Type of recommendation: no recommendation; Evidence quality: low; Strength of recommendation: not applicable).

Note: While recent preliminary evidence suggests a potential for benefit from exercise, acupuncture, and scrambler therapy, larger sample–sized definitive studies are needed to confirm efficacy and clarify risks.

Literature Review Update and Analysis for Treatment of CIPN

Exercise. Current data from an RCT mildly suggest that exercise is a feasible, safe, and promising supportive measure for patients with cancer experiencing CIPN. The trial randomly assigned 45 patients with established CIPN to a 10-week home-based muscle strengthening and balancing exercise program versus usual care. The patients in the exercise group experienced a significant reduction in neuropathic pain scores ($P < .0001$) and improvement in Functional QOL ($P = .0002$), Symptom QOL ($P = .0003$) and Global Health Status QOL ($P = .004$) compared with those randomly assigned to the usual-care group.[52] The lack of an active control group diminishes the strength of the findings. Another small trial evaluated patients with metastatic colorectal cancer randomly assigned to an exercise program versus a wait-list control group.[36] Those receiving exercise had relatively stable CIPN scores over time, while the wait-list control group's CIPN worsened.

Acupuncture. Five trials evaluating the efficacy of acupuncture for the treatment of CIPN were identified,[53-55] including 1 trial that evaluated electro-acupuncture[56] and another that evaluated acupuncture combined with methylcobalamin.[57] A randomized assessor-only–blinded controlled trial of acupuncture twice weekly for 8 weeks versus a wait-list control group involving 87 patients with cancer reported significant changes at 8 weeks in pain measured using the Brief Pain Inventory (BPI).[53] Significant improvements in clinical neurologic assessment, QOL domains, and symptom distress were also reported (all $P < .05$). Improvements in pain interference, neurotoxicity-related symptoms, and functional aspects of QOL were sustained in a 14-week assessment ($P < .05$), as were physical and functional well-being at a 20-week assessment ($P < .05$).

A pilot trial involving 40 women with stage I-III breast cancer and grade $\geq$ 1 CIPN after taxane-containing adjuvant chemotherapy investigated immediate acupuncture versus a wait-list control.[54] At 8 weeks, participants in the treatment arm experienced significant improvements in the Patient Neurotoxicity Questionnaire (PNQ) sensory score ($P = .01$), FACT-NTX summary score ($P = .002$), and BPI–Short Form pain severity score $P = .03$) compared with those in the control arm. No serious adverse effects were observed.

Another pilot trial randomly assigned 33 adult patients with cancer and CIPN into 2 groups (control and acupuncture: treated with 10 sessions, twice a week).[55] Statistically significant differences were reported in physical ($P = .03$) and function ($P = .04$) domains of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 when comparing between control and acupuncture groups. NCI CTCAE Scale and neuropathy sensory symptoms were also improved in the acupuncture group between pretreatment and 5 weeks post-treatment ($P = .01$), whereas no such differences were detected in the control group ($P = .11$). The use of electro-acupuncture was not superior to placebo in a randomized trial of 59 patients with CIPN.[56] The trial failed to show efficacy compared with placebo, as determined by using a predefined statistical threshold at the first interim analysis.

Another trial in 98 patients compared acupuncture combined with methylcobalamin to methylcobalamin alone and found that after 3 cycles of therapy the pain was significantly mitigated in the methylcobalamin plus acupuncture group.[57] Visual analogue scale (VAS) pain scores decreased more in the methylcobalamin plus acupuncture group than the methylcobalamin control group ($P < .01$).

Duloxetine and pregabalin. Two duloxetine trials were published after the initial ASCO CIPN guideline publication.[48,58] One trial randomly assigned patients with CIPN to 3 pharmacotherapy groups: venlafaxine, duloxetine, and placebo.[48] The authors reported decreased neuropathy in the venlafaxine and duloxetine groups, with a better reduction in the duloxetine group compared with venlafaxine group ($P < .05$). In another open-label, randomized, crossover study, 34 patients with cancer were randomly assigned to receive duloxetine (20 mg/d orally for the first week and 40 mg/d for the next 3 weeks) or vitamin B12 (1.5 mg/d orally for 4 weeks).[58] After a 2- to 4-week washout period, treatment was crossed over for another 4 weeks. Decreases in the mean VAS scores for numbness and pain were seen during the periods of duloxetine administration. Significant differences were observed between the duloxetine-first and the vitamin B12-first groups with respect to numbness ($P = .03$) and pain ($P = .04$) at 4 weeks after administration.

In January 2020, a trial was published that randomly assigned patients with paclitaxel- or docetaxel-associated CIPN to receive duloxetine versus pregabalin, with 40-42 patients per arm. They reported a $\geq$ 33% improvement of visual analog scores in the duloxetine and pregabalin arms at 6 weeks of 38% and 93%, respectively ($P < .001$).[59] The majority of the patients in both arms started their treatment while they were receiving chemotherapy, and some of this improvement may have been related to chemotherapy discontinuation.

Scrambler therapy. Two randomized trials evaluating scrambler therapy, an electrocutaneous treatment approach, were found.[60,61] One randomized sham-controlled phase II trial in 33 patients who received 30-minute sessions of scrambler therapy (ST) or sham treatment found no significant differences between the sham and the experimental ST group for BPI average pain or the EORTC CIPN-20.[60]

The second phase II trial randomly assigned patients with CIPN symptoms for at least 3 months to receive ST or transcutaneous electrical nerve stimulation (TENS) for 2 weeks. In 46 evaluable patients, twice as many ST-treated patients had at least a 50% documented improvement during the 2 treatment weeks from their baseline pain, tingling, and numbness scores when compared with the TENS-treated patients (from 36%-56% compared with

16%-28% for each symptom).[61] Global Impression of Change scores for "neuropathy symptoms," pain, and QOL improved similarly. Moreover, patients in the ST group were more likely than those in the TENS group to recommend their treatment to other patients, during both the 2-week treatment period and the 8-week follow-up period ($P < .0001$).[61] The publication did not report any substantial adverse events.[62]

Oral mucosal cannabinoid extract. A small, randomized, placebo-controlled clinical trial of 18 patients evaluated the role of nabiximols, an oral mucosal cannabinoid spray, for chemotherapy-induced neuropathic pain.[63] In this crossover clinical trial, 16 of the 18 randomly assigned patients completed the study. Noting the small number of patients, there was no suggestion of differential benefits in neuropathy scores between the active and placebo agents. Yet, there was more evidence of toxicity (fatigue, dry mouth, dizziness, and nausea) in the patients receiving the cannabinoid preparation, decreasing interest in this approach.

Topical amitriptyline/ketamine. A topical 4% amitriptyline/2% ketamine preparation was studied as a treatment of established chemotherapy neuropathy in a randomized, placebo-controlled trial involving 462 patients.[64] Patients with average 7-day pain, numbness, and tingling ratings of at least 4 on an 11-point numeric rating scale were eligible for enrollment in the study. Topical amitriptyline/ketamine showed no effect on 6-week CIPN scores (adjusted mean difference, −0.17; $P = .363$), and this trial did not support that using this topical preparation alleviated chemotherapy-induced pain, numbness, or tingling.

Clinical interpretation regarding the treatment of established CIPN. Additional data, which have become available since the previous ASCO CIPN guideline, further support the utility of duloxetine for treating established painful CIPN. Conversely, there have not been any further clinical trials to strongly support the utility of tricyclic antidepressants, gabapentinoids, or topical amitriptyline/ketamine/baclofen, decreasing the tepid support that was provided for these 3 therapeutic approaches in the initial ASCO CIPN guideline. In addition, newer published reports do not provide support for a topical amitriptyline/ketamine preparation or an oral mucosal cannabinoid product.

Although proof of benefit has not been provided, data suggestive of benefit support that 3 approaches (scrambler therapy, acupuncture, and exercise) may diminish established CIPN symptoms and appear to be reasonably safe. Further research is needed to better delineate the utility, or its lack thereof, of these approaches in treating established CIPN.

DISCUSSION

The current review found no additional studies supporting the use of any preventative approach for neuropathy. In contrast with the promising original guideline commentary regarding venlafaxine as a preventative agent, longer follow-up data do not support its use.[47]

For treatment of established painful neuropathy, duloxetine remains the sole recommended treatment. Along with the data demonstrating that duloxetine decreases CIPN pain, there is a suggestion from exploratory analyses that it also decreases nonpainful CIPN symptoms.[58,65] When patients stop duloxetine, it should be tapered slowly, as stopping abruptly can lead to withdrawal symptoms.

Acetyl-L-carnitine data were inconclusive for the treatment of established neuropathy at the time of the initial ASCO guideline publication. A new larger trial reported that there was no benefit for acetyl-L-carnitine for treating chemotherapy-induced neuropathy. Consequently, the current updated guideline recommends against acetyl-L-carnitine for the treatment of established chemotherapy-induced neuropathy.[14]

There were 3 treatments that were inconclusive in the original guideline but "reasonable to try in some situations," namely tricyclic antidepressants, gabapentinoids, and a topical gel treatment containing baclofen, amitriptyline, and ketamine. Although data regarding these 3 treatment options remain inconclusive, there is waning enthusiasm regarding them.

Regarding the tricyclic antidepressants, the previous guideline indicated that tricyclic antidepressant use was reasonable to try, primarily on the basis of their utility in other neuropathy situations, but not on the basis of any positive randomized clinical trials demonstrating any utility of this drug class for treating established CIPN. Currently, the use of tricyclic antidepressants does not appear to be common, because of their lack of established benefit and/or their unfavorable side effects.

Regarding topical baclofen, amitriptyline, and ketamine, the previous guideline noted that a placebo-controlled trial was promising. However, there are reasons to be less enthusiastic about this approach now: (1) no additional trials have been conducted; (2) there is not an US Food and Drug Administration–approved product available, and the only way to get this treatment is to have it compounded; and (3) there was a subsequent publication of a negative trial that studied topical amitriptyline and ketamine.[64] However, the lack of baclofen in this latter preparation may explain the negative finding of the study.

The suggestion in the initial ASCO CIPN guideline that gabapentinoids might be helpful and worth trying for chemotherapy-induced neuropathy was also primarily based on gabapentinoid efficacy against other types of neuropathies, like diabetic neuropathy. Presently, this endorsement is harder to support. With the 1 older placebo-controlled clinical trial that showed no benefit for gabapentin for the treatment of chemotherapy-induced peripheral neuropathy,[66] 2 subsequent trials investigating pregabalin as an agent to prevent chemotherapy-induced neuropathy (1 for paclitaxel[43] and 1 for oxaliplatin [ClinicalTrials.gov Identifier: NCT00380874]) failed to provide evidence of benefit. Although prevention trials are certainly

different from treatment trials, if pregabalin was given continuously while the patient developed neuropathy in a prevention trial, one would have expected to see a decrease in the severity of neuropathic symptoms if it was truly beneficial for treating established neuropathy. In contrast to these negative gabapentinoid data, 1 trial[59] suggests that pregabalin was helpful. Confirmation of these data is necessary before endorsement of routine use of gabapentinoids for treating established CIPN.

Historically, the first known report on using gabapentin for chemotherapy-induced neuropathy came from Italian authors at the 2000 ASCO annual meeting, entitled "Oxaliplatin-induced Neuropathy: Could Gabapentin be the Answer?"[67] This report describes the use of gabapentin in 7 patients who developed neuropathy while receiving oxaliplatin. With the initiation of neuropathy, gabapentin was given at 100 mg twice per day. Clinicians could increase gabapentin to 100 mg 3 times daily if the lower daily dose did not resolve symptoms. The abstract reported there was a disappearance of neuropathy symptoms, which continued even with the use of up to 14 total oxaliplatin doses. This work is not available in manuscript form. In retrospect, it does not seem biologically plausible that this very low dose of gabapentin (given that target doses of this drug can be $\geq$ 3,000 mg/d) could have had such a dramatic benefit. A body of other published articles regarding gabapentin for treating CIPN (ranging from case reports to case series to 1 randomized placebo-controlled trial)[66,68-74] do not, on the whole, support the utility of gabapentin for treating established CIPN.

Notably, some insurance companies require that patients with CIPN receive a gabapentinoid agent before allowing the use of duloxetine.[75] Additional support for this contention comes from a recent article reporting that on insurance claims data the use of gabapentinoids (gabapentin or pregabalin) was more than 8-fold higher than was the use of duloxetine in patients who had recently received neurotoxic chemotherapy.[76] This contradicts the recommendations of the previous and current ASCO CIPN guidelines.

Although the current guideline is primarily focused on means of preventing CIPN and/or treating established CIPN, CIPN can involve physical dysfunction; patients with CIPN have balance troubles and a higher chance of falling.[77,78] Therefore, it is reasonable to consider physical therapy and/or occupational therapy approaches for patients with such CIPN-related disabilities.

A summary of the recommendations is provided in Table 3.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting and also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

Inconsistent subjective and objective outcome measures, choice of control group, and duration of exposure have resulted in challenges in interpreting some of the prior studies. NCI-sponsored studies are ongoing to better define the phenotype of CIPN, to ensure consistency in outcome measures from study to study going forward.

Better interventions are needed to prevent CIPN. Ongoing and planned trials will, likely, better clarify the role of exercise, compression therapy, cryotherapy, and other targeted interventions. Several planned and/or ongoing preclinical studies are evaluating the role of neuronal transport, neuroprotection, neuro-inflammation, serotonin-norepinephrine reuptake, nociceptor sodium channel inhibition, mitochondrial enzymes, and oxidative stress.[79-81] Many of the above agents target DNA damage related to inflammation, reactive oxygen species, and oxidative stress, supporting this as a thematic target for prevention of CIPN.

Better agents are also needed to treat established CIPN. Ongoing and planned clinical trials should better clarify the role of exercise, acupuncture, scrambler therapy, and other targeted interventions. Topical therapies such as capsaicin might also be further explored.[82]

Clinicaltrials.gov currently lists > 100 clinical trials related to CIPN that are actively accruing patients or in development. We hope that results from these trials will lead to new means of preventing and/or treating CIPN.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/survivorship-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Patient-Clinician Communication[83] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.01399.

ACKNOWLEDGMENT

We thank Ting Bao, MD, DABMA, MS, Zoneddy Dayao, MD, Emily Tonorezos, MD, MPH, and Jørn Herrstedt MD, DMSc, and the Clinical Practice Guidelines Committee for their thoughtful reviews and insightful comments on this guideline. All Appendices and Acknowledgment material (including the table of Expert Panel members) are online-only. They will appear on JCO website online but not in the print version.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Patents, Royalties, Other Intellectual Property: I have a number of antibodies that have been licensed from Indiana University School of Medicine that are sold by various companies. The royalties come back to the school and I share in some of them. I receive some royalties from licensed technology to Apexian Pharmaceuticals and could eventually receive royalties from Ocuphire Pharma if milestones are met. Ocuphire is an eye company and not cancer related. I have not received any royalties from these units at this time beyond consulting as disclosed. Apexian licensed my IP and then sublicensed IP to Ocuphire for the eye.

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Open Payments Link: https://openpaymentsdata.cms.gov/physician/202382/general-payments

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers Guideline Update Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Charles L. Loprinzi, MD (co-chair)	Mayo Clinic, Rochester, MN	Medical oncology
Dawn L. Hershman, MD, MS (co-chair)	Columbia University Medical Center, New York, NY	Medical oncology
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Shelby Terstriep, MD	Sanford Health, Fargo, ND	Medical oncology
Judith A. Paice, PhD, RN	Northwestern University, Chicago, IL	Nursing/pain
Guido Cavaletti, MD, PhD	University of Milano-Bicocca, Monza, Italy	Neurology/pain
Daniel L. Hertz, PharmD, PhD	University of Michigan, Ann Arbor, MI	Clinical pharmacology
Mark R. Kelley, PhD	Indiana University School of Medicine, Indianapolis, IN	Translational research
Antoinette Lavino, RPh, BCOP	Oncology Pharmacist, PGIN Member, Mass General North Shore Cancer Center, Danvers, MA	Community oncology
Ellen M. Lavoie Smith, PhD	University of Michigan, Ann Arbor, MI	Nursing
Cynthia Chauhan, MSW, Patient Advocate	Wichita, KS	Patient representative
Mary Lou Smith, JD, MBA, Patient Advocate	Research Advocacy Network, Plano, TX	Patient representative
Christina Lacchetti, MHSc	ASCO, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

Abbreviation: PGIN, Practice Guideline Implementation Network.