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

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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.

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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.14

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
- Diethylthiocarbamate (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

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an “as is” basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

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/nwc). 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. 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>
<thead>
<tr>
<th>Investigated Compounds</th>
<th>Study Design</th>
<th>Agent</th>
<th>Evaluated Patients (No.)</th>
<th>Interventions</th>
<th>Toxicity</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asety-l-carnitine</td>
<td>Doub e-b nd random zed phase study</td>
<td>Taxane-based chemotherapy</td>
<td>409</td>
<td>1 000 mg 3 times a day</td>
<td>ALC group had a statistically significant (P = 0.01) greater worsening of NTX scores of −1.23 points (95% CI: 2.63 to −1.50)</td>
<td></td>
</tr>
<tr>
<td>Campone et al. 14</td>
<td>Doub e-b nd random zed phase study</td>
<td>Sepp 01</td>
<td>150</td>
<td>1 000 mg every 3 days</td>
<td>No significant differences between the 2 treatment arms for peripheral neuropathy over a median duration of treatment was a medium</td>
<td></td>
</tr>
<tr>
<td>Alpha- p c ac d</td>
<td>Phase random zed double-b nd p acebo- contro ed trial</td>
<td>Cspat n or oxapat n</td>
<td>243</td>
<td>600 mg 3 times a day</td>
<td>No significant differences between the 2 treatment arms for peripheral neuropathy On y 70% of 243 patients (29%) completed the study</td>
<td></td>
</tr>
<tr>
<td>Calcium and magnesium</td>
<td>Systematic review</td>
<td>Oxa 01</td>
<td>604 patients from 6 trials</td>
<td>CaMg nfu sions</td>
<td>nct of grade 2 neuropathy RR 0.81, 95% CI 0.60 to 1.11; nct of chronic neurotoxicty for severe grades pooled RR of 0.95 (95% CI: 0.69 to 1.32)</td>
<td>Concluded that CaMg was not beneficial for decreasing oxapatin-induced neuropathy</td>
</tr>
<tr>
<td>Han et al. 21</td>
<td>Randomized trial</td>
<td>Oxa 01</td>
<td>19</td>
<td>1 g of each of 5 before and after chemotherapy</td>
<td>No acute neuropathy differences between the 2 study arms No differences in EMG motor nerve hyporeactable scores between arms</td>
<td></td>
</tr>
<tr>
<td>Calcium manganof p r</td>
<td>P acebo-contro ed random zed phase study</td>
<td>Oxa 01</td>
<td>173</td>
<td>Ca manganof p r was given as a 5-m neut n fusions on 10 m nutes before oxa 01</td>
<td>Ca manganof p r-treated patients (a 3 doses pooled) did not have significant differences in physical-graded neurotoxicity (OR: 0.62, 95% CI: 0.46 to 1.00) but had significantly fewer sensory symptoms in the Leonard scale (cyc e 1-8 mean: 1.9 vs 3.0; P &lt; 0.05 and during follow-up after 3 and 6 months mean: 3.5 vs 7.3; P &lt; 0.01)</td>
<td></td>
</tr>
<tr>
<td>U-camos ne</td>
<td>Randomized contro ed p ol trial</td>
<td>Oxa 01</td>
<td>65</td>
<td>Arm A: 31 patients received FOLFOX-6 regimen (oxapatin FU and 5-fluorouracil) arm B: 34 patients received FOLFOX-6 regimen and dacarbazine U-camos ne (500 mg) a ong the treatment per ed</td>
<td>Neuropathy grade 2 arm A: 19 patients (61.3%) arm B: 1 patient (3.3%)</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Invest gat on /Authors</th>
<th>Study Des gn</th>
<th>Neurotox c Chemotherapy Agent</th>
<th>Patients (No.)</th>
<th>Intervent on Dose</th>
<th>Incidence/Sever ty of Neuropathy Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hana et al.</td>
<td>Prospect ve self-contro ed cont ra</td>
<td>Pac taxe</td>
<td>36</td>
<td>Each patient wore fl exible FGs and socks on the dominant hand and foot from 15 minutes before pac taxe adm inistration to 15 minutes after the infusion was complete. FGs were replaced after the first 45 minutes. The random nant s were acted as the untreated contro.</td>
<td>Incidence of objective and subject ve C PN signs was c n a y and stat st ca y s gnificant y lower on the intervent on s de than on the contro. Hand OR 20.00 95% C 3.20 to 82.96 P &lt; 0.01 foot OR nfin te 95% C 3.32 to nfin te P &lt; 0.01 warm sense hand OR 9.00 95% C 1.25 to 39.48 P = 02 foot OR 5.00 95% C 1.07 to 46.93 P = 04.</td>
</tr>
<tr>
<td>Bejers et al.</td>
<td>Prospect ve random zed tr a</td>
<td>Pac taxe</td>
<td>180</td>
<td>Pat ents were random y ass gned between wear ng FGs on both hands during treatment or not wear ng FGs. TT analyses. EORTC C PN20 subsca es no stat st ca y s gnificant d fferences between intervent on and contro groups. n cryotherapy arm ess t ng ng n fingers/ hands (P = 0.05) ess trouble open ng a jar (P = 04). EORTC QLQ-C30 qua ty of fe better (P = 03).</td>
<td>34% d scont nued the FGs before end of chemotherapy ma ny due to d scomfort. The EORTC C PN20 subsca es nc ude data on ower extrem t es wh ch were not coo ed n th s tr a.</td>
</tr>
<tr>
<td>Ruddy et al.</td>
<td>Prospect ve random zed p ot phase study</td>
<td>Pac taxe</td>
<td>42</td>
<td>Hands and feet were coo ed start ng 15 minutes before each pac taxe dose and cont nued for 15 minutes after each dose was complete.</td>
<td>No d fference n C PN20 scores between the study arms but cross-study compar son ssuggested bene t from cryotherapy.</td>
</tr>
<tr>
<td>McCarthy et al.</td>
<td>Prospect ve random zed study</td>
<td>Docetaxe</td>
<td>53</td>
<td>Part c pants acted as the own contro with the frozen ge g ove worn on 1 random y ass gned hand start ng 15 minutes before infusion and cont nuing unt 15 minutes after completion of treatment.</td>
<td>No s gnificant d fferences were determ ned between hand cond t ons in terms of t meto event or n terms of tox ty n g oved and non g oved hands. 60% w thdrawa rate due to pat ent d scomfort w th the intervent on.</td>
</tr>
<tr>
<td>Band a et al.</td>
<td>Interne y contro ed p ot tr a</td>
<td>Pac taxe</td>
<td>20</td>
<td>Pat ents underwent mb hypotherm a of 1 eg for a durat on of 3 hours with every pac taxe nfus on w th the contra atera mb used as contro. Grade 3 PN occurred in 2 pat ents (10%) grade 2 n 2 (10%) and grade 1 n 12 (60%). S gnificant corre at on was observed between amount of sk n coo ng and motor nerve amp tude preservat on at 6 months (P &lt; 0005). Sensory ve oc ty and amp tude in the coo ed mbs were ess preserv ed than in the contro mbs but the d fference d d not atta n stat st ca s gnificant. We to erated w th no premature term nat on of coo ng due to mb erance.</td>
<td></td>
</tr>
<tr>
<td>Kanbayash et a</td>
<td>Phase e self-contro ed contro ed cont ra</td>
<td>Pac taxe</td>
<td>38</td>
<td>Dur ng chemotherapy patients wear an FG on one hand and 2 SGs of the same size (e 1 size sma er than the size that best fits the hand) on the other hand.</td>
<td>Freq uencies of CTCAE grade 2 was 18.4% n both groups Freq uencies of PNQ grade 2 per phera neuropath es was 2.6% n both groups. No d fference was d tected between FG and SG groups n PNQ sensory neuropathy (P = 32 10). PNQ motor neuropathy (P = 51 10) or tota FACT-T score (P = 67 93) at each eva uat on t me. Authors conc uded that both approaches appeared to have sm ar benefits.</td>
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<table>
<thead>
<tr>
<th>Investigator/Authors</th>
<th>Study Design</th>
<th>Neurotoxic Chemotherapy</th>
<th>Evaluated Patients (No.)</th>
<th>Intervent on Dose</th>
<th>Incidence/Severity of Neuropathy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsubok et al. a,b</td>
<td>Randomized controlled trial</td>
<td>Paclitaxel</td>
<td>42</td>
<td>Each patient wore 2 SGs on the dominant hand; both were 1 size smaller than the size that was used to fit the patient’s hand. The dominant hand served as a control (ie, did not wear SGs or anything else)</td>
<td>Compared with the control hands, the SG-protected hands had a noted reduction in the incidence of grade 2 or higher PN over the treatment cycles. P &lt; 0.001; fewer patients had grade 4 PN responses. Motor and sensory neuropathy decreased over the course of treatment. CTC grading: grade 2 PN from 76% to 21%</td>
<td>During the administration of nab-PTX: 9 patients (21%) were admitted to the study for treatment-related neuropathy.</td>
</tr>
<tr>
<td>Griffiths et al. a,b</td>
<td>Randomized controlled trial</td>
<td>Paclitaxel</td>
<td>29</td>
<td>Patients wore a gauze and a cotton glove over their hands, and a sock with a rubber band around the ankle, to accommodate the size of the glove and sock. There was no significant difference in NPS scores between treated and untreated hands (P &gt; 0.05).</td>
<td>There were no significant differences in NPS scores between treated and untreated hands (P &gt; 0.05).</td>
<td>Ten (34%) patients were enrolled in the study for treatment-related neuropathy.</td>
</tr>
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</table>

### Exercise

<table>
<thead>
<tr>
<th>Investigator/Authors</th>
<th>Study Design</th>
<th>Neurotoxic Chemotherapy</th>
<th>Evaluated Patients (No.)</th>
<th>Intervent on Dose</th>
<th>Incidence/Severity of Neuropathy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimmer et al. a,b</td>
<td>Randomized controlled trial</td>
<td>Various regimens for patients with metastatic colorectal cancer</td>
<td>30</td>
<td>Interventions included 8-week supervised exercise program, including endurance exercises and balance training.</td>
<td>Neuropathy symptoms were assessed using the University of California, San Francisco (UCSF) Pain and Fatigue Evaluation Tool. Changes in CTRC were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).</td>
<td>Changes in CTRC were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).</td>
</tr>
<tr>
<td>Keckner et al. a,b</td>
<td>Randomized controlled trial</td>
<td>Taxane-based chemotherapy</td>
<td>355</td>
<td>Interventions included chemotherapy plus EXCAP at standard doses, with or without moderate-intensity home-based 6-week endurance exercise programs.</td>
<td>Exercise significantly reduced CTRC symptoms of fatigue and sleep disturbances.</td>
<td>Exercise significantly reduced CTRC symptoms of fatigue and sleep disturbances.</td>
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### TABLE 1. New Randomized Controlled Trials Regarding the Prevention of C PN Since the nita ASCO Guidance (contd)

<table>
<thead>
<tr>
<th>Investigator(s) / Authors</th>
<th>Study Design</th>
<th>Neurotoxicity Agent</th>
<th>Patients (No.)</th>
<th>Intervention</th>
<th>Incidence/Severity of Neuropathy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM-1</td>
<td>Randomized</td>
<td>Oxa patin</td>
<td>120</td>
<td>100 mg once/day y V</td>
<td>Less neuropathy in the investigational treatment arm compared with the control group</td>
<td>Can an-reported neuropathy not patient-reported. Lack of a placebo arm introduces potential bias.</td>
</tr>
<tr>
<td>Su et al</td>
<td>Randomized</td>
<td>Taxanes</td>
<td>206</td>
<td>80 mg day -1 to day 2</td>
<td>Function assessment of cancer treatment neuropathy subgroups GM-1 43.3 (95% C.I. 43.1 to 43.5) Placebo 34.3 (95% C.I. 33.8 to 34.9) mean difference 8.96 (95% C.I. 8.4 to 9.5 P &lt; 001) Grade ≥ 1 per patient neuropathy n CTC-AE v4 GM-1 14.3% placebo 100% P &lt; 001 n incidence of grade ≥ 1 neuropathy by ECOG Sensory neuropathy GM-1 26.4% vs placebo 97.8% P &lt; 001 Motor neuropathy GM-1 20.9% vs placebo 81.5% P &lt; 001</td>
<td>Possible reversion of C PN 3 months after taxane completion as has not been observed in other trials.</td>
</tr>
</tbody>
</table>

| Goshalikgan               | Systematic review and meta-analysis | —                | 397 from 5 trials | —                | Reduced incidence of C PN grade ≥ 1 RR 0.43 95% C.I. 0.27 to 0.66 Reduced incidence of C PN grade ≥ 2 not statistically significant Reduced incidence of C PN grade ≥ 3 RR 0.42 95% C.I. 0.25 to 0.71 | Authors concluded that given the low quantity and insufficient amount of the evidence, use of goshalikgan as standard of care is not currently recommended. |

| Metformin                 | Randomized   | Oxa patin           | 40             | —                | NC-CTCAE peripheral neuropathy grade at the end of 12th cycle there were significantly fewer patients with grade ≥ 2 neuropathy in the metformin arm compared with the control arm (60% vs 95%; P = 0.009). The No-12 questionnaire at the end of the 6th cycle and on the 12th cycle metformin group showed significantly higher mean scores than control group (37.8 vs 34.5 P = 0.001 and 240 vs 192 P < 0.001 respectively). The BP- SF worst pain at the end of 11th and 12th cycles metformin group showed significantly lower mean pain scores than control group (6.4 vs 6.9 P = 0.01 and 6.7 vs 7.3 P = 0.001, respectively). |

(continued on next page)
### TABLE 1. New Randomized Controlled Trials Regarding the Prevention of C-PN Since the NCI ASCO Guidelines (Cont'd)

<table>
<thead>
<tr>
<th>Investigator / Authors</th>
<th>Study Design</th>
<th>Neurotoxic Chemotherapy Agent</th>
<th>Exposed Patients (No.)</th>
<th>Interventional Dose</th>
<th>Incidence / Severity of Neuropathy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Andrade et al.</td>
<td>Randomized double-blinded placebo-controlled</td>
<td>Oxaliplatin 143</td>
<td>3 days before and 3 days after oxaliplatin infusion</td>
<td>Pain intensity: pregabalin 1.08 (96% C 0.79 to 1.26) placebo 0.85 (95% C 0.64 to 1.06) Not significant. Scores from the BCMPQ-DN-4 NPS and NCS and de-effect profile are and incidence of death d do not differ between groups. QOL score: pregabalin group: 79.4 ± 20.6 placebo 76.9 ± 23.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shinde et al.</td>
<td>Placebo-controlled</td>
<td>Paclitaxel 46</td>
<td>75 mg/d</td>
<td>Not enough positive evidence to support a phase trial</td>
<td></td>
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</tr>
<tr>
<td>Gabapentin</td>
<td>Randomized double-blinded placebo-controlled</td>
<td>Paclitaxel 40</td>
<td>300 mg, 3 times a day</td>
<td>Difference in neuropathy grade between the gabapentin and control group were statistically significant in favor of gabapentin in each treatment cycle (P &lt; 0.04). Change in baseline nerve conduct rate after 4 cycles of paclitaxel was statistically significant over the gabapentin group compared with placebo (sura 17.7 ± 37.2% v 61.0% ± 48.0% P = 0.04 peronea nerve 21.9 ± 41.5% v 62.5% ± 53.5% P = 0.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Placebo-controlled</td>
<td>Oxaliplatin 50</td>
<td>37.5 mg twice a day</td>
<td>Not enough positive evidence to support a phase trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B</td>
<td>Placebo-controlled</td>
<td>Oxaliplatin 47</td>
<td>1 capsule twice a day of Vitamin B compared with oxaliplatin 100 mg of thiamine 20 mg of riboflavin 100 mg of niacin 165 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 taurine</td>
<td>TNS demonstrated that the Vitamin B group did not significantly reduce the incidence of C-PN compared with placebo (P = 0.73). Statistically significant was achieved for pain perception sensory peripheral neuropathy (12 weeks P = 0.05; 16 weeks P = 0.05)</td>
<td></td>
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</tr>
<tr>
<td>Investigator</td>
<td>Study Design</td>
<td>Neurotropic Chemotherapy</td>
<td>Patient Events</td>
<td>Intervention Dose</td>
<td>Incidence/Severity of Neupathy</td>
<td>Other</td>
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<tr>
<td>Huang et al.</td>
<td>Systematic review and meta-analysis</td>
<td>P atnum-based therapy, pac taxe-based therapy, and various other chemotherapeutic agents</td>
<td>363 from 6 studies</td>
<td>300 mg/day (1 study) 300 mg twice/day (G study) 400 mg/day (1 study)</td>
<td>Incidence of C.P.N. RR 0.55 95% CI 0.29 to 1.06, P = 0.07 RR n = 34, C.P.N. RR n = 23 Subgroup analysis of chemotherapy type, C.P.N. RR = 0.59 to 1.02, P = 0.038</td>
<td>Four of the 6 included studies assessed the safety of vani n e dur ng chemotherapy and no adverse events were observed</td>
</tr>
<tr>
<td>Saeh et al.</td>
<td>Prospective randomized controlled study</td>
<td>Oxaplatin</td>
<td>65</td>
<td>400 mg/day</td>
<td>Mean percent neuropathy score changes (mean ± SD) after treatment: group 1: 6.37 ± 2.85, group 2: 6.57 ± 2.94, P = 0.78</td>
<td></td>
</tr>
<tr>
<td>Green et al.</td>
<td>Randomized sham-controlled study</td>
<td>Taxanes</td>
<td>63</td>
<td>Selected acupuncture points were attached to 2 gloves connected to an electro-stimulator that delivered 2 Hz of 1.5 mA at a rate of 20 Hz. Needles were not attached to the electro-stimulator.</td>
<td>Percent neuropathy score changes (mean ± SD) after treatment: group 1: 6.37 ± 2.85, group 2: 6.57 ± 2.94, P = 0.45</td>
<td></td>
</tr>
<tr>
<td>Wang et al.</td>
<td>Phase 1 randomized controlled trial</td>
<td>Oxaplatin</td>
<td>66</td>
<td>Intervention n = 100 mg twice/day</td>
<td>There was no observed significant symptom reduction on numbness tingling n = 23. There was no observed significant symptom reduction on numbness tingling n = 23.</td>
<td></td>
</tr>
<tr>
<td>Pechman et al.</td>
<td>Randomized phase study</td>
<td>Paclitaxel</td>
<td>47</td>
<td>Intervention n = 100 mg twice/day</td>
<td>There were no remarkable changes noted in the neuropathy scores of the EORTC QLQ-C30 and QLQ-C15.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALC: acetylcarnitine; BPSF: Brief Pain Inventory; Short Form; CPT: Chemotherapy-induced peak pharay; CTA: CTCAE; CR: Common Terminology Criteria for Adverse Events; DN-4: Douleur Neuropathique; EORTC: European Organization for Research and Treatment of Cancer; FACT: Functional Assessment of Cancer Therapy; FOLFOX: fluorouracil, leucovorin, and oxaplatin; FUS: frozen and gavage; FU: fluorouracil; GM-1 ganglioside; M: monoclonal; MPQ: McGill Pain Questionnaire; NC: National Cancer Institute; NCS: Nerve Conduction Studies; NPS: Neuropathy Symptom Inventory; NTX: neutrophil count; OR: odds ratio; P-APS: Paclitaxel-associated acute pain syndrome; PN: periphern neuropathy; PNQ: Paclitaxel-induced neuropathy; QLQ-C30: Quality of Life Questionnaire; QOL: Quality of Life; RR: relative risk; RR: relative risk; SG: survival; TNS: Tumor Necrosis Score; TNS: Tocilizumab; V: vani.
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, acetylcarnitine for the prevention of CIPN in patients with cancer (Type of recommendation: evidence based, harms outweigh benefits; Evidence quality: low; Strength of recommendation: not applicable).

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
- Oxo-carbapine
- Recombinant human leukemia inhibitory factor
- Venlafaxine
- Vitamin B
- Vitamin E

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

Literature Review Update and Analysis on Prevention

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. 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 reported data on the use of acetyl-l-carnitine for preventing sago pilone-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. 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.

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.

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. Two older pooled analyses identified from Xu et al and Wen et al, which did not come to the same conclusion, should be
<table>
<thead>
<tr>
<th>Investigational Agents/ Authors</th>
<th>Study Design</th>
<th>Neurotoxic Chemotherapy Agent</th>
<th>Evaluable Patients (No.)</th>
<th>Neuruphathy Outcomes</th>
<th>Methods</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duroplex and pregabalin</td>
<td>Randomized, controlled trial of duroplex and varenflaxine</td>
<td>Varenflaxine</td>
<td>156</td>
<td>Grades of neuropathy outcomes decreased significantly in varenflaxine and duroplex groups. Reduction was more considerable in duroplex group compared with varenflaxine group (P &lt; 0.05).</td>
<td>Patient-reported outcomes and neurologic assessments</td>
<td>Varenflaxine was used in the control arm. Crossover data after a washout period; a supported duroplex benefit.</td>
</tr>
<tr>
<td>Hrayama et al. 55</td>
<td>Open-label, randomized crossover study</td>
<td>Varenflaxine</td>
<td>34</td>
<td>Significant decreased VAS score in duroplex, pain (P = 0.04) in numbness (P = 0.03). No AEs grade &gt; 2 by CTCAE</td>
<td>Patient-reported outcome</td>
<td>Varenflaxine was used in the control arm. Crossover data after a washout period; a supported duroplex benefit.</td>
</tr>
<tr>
<td>Sahar et al. 57</td>
<td>Randomized, controlled trial of duroplex and pregabalin</td>
<td>Taxanes</td>
<td>82</td>
<td>Both arms showed statistically significant decrease in C-FN from baseline to pregabalin was reported to be significantly better than duroplex.</td>
<td>Patient-reported outcomes and CTCAE evaluations</td>
<td>Most patients were started on this therapy while they were receiving chemotherapy. Confirmation of these results needed given other results of other reported gabapentin trials.</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Phase II, randomized, double-blind, placebo-controlled trial</td>
<td>Topiramate</td>
<td>462</td>
<td>No observed benefit from treatment</td>
<td>Patient-reported outcome</td>
<td></td>
</tr>
<tr>
<td>Oral mucosa cannabinoid extract</td>
<td>Randomized, placebo-controlled crossover study</td>
<td>Varenflaxine</td>
<td>16</td>
<td>No statistically significant difference between the treatment and the placebo groups on the NRS-P.</td>
<td>No statistical significance</td>
<td>Low power</td>
</tr>
<tr>
<td>Scrambler therapy</td>
<td>Randomized, placebo-controlled crossover study</td>
<td>Variety</td>
<td>46</td>
<td>Baseline pain, tingling and numbness scores compared with TENS-treated patients: twice as many scrambled-treated patients had ≤ 50% documented improvement during the 2 treatments. Patients in the scrambled group were more than 50% of the TENS group to recommend their treatment to other patients during both the 2-week treatment period and the 6-week follow-up period (P &lt; 0.001).</td>
<td>Patient-reported outcomes</td>
<td>Mn monotherapy was observed</td>
</tr>
<tr>
<td>Smith et al. 50</td>
<td>Randomized, sham-controlled phase trial</td>
<td>Variety</td>
<td>46</td>
<td>Average pain BP and EORTC C-PN20 no statistically 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 C-FN-20 at 2 months in the real group (P = 0.14).</td>
<td>Patient-reported outcomes</td>
<td></td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Randomized, placebo-controlled trial</td>
<td>Taxanes</td>
<td>40</td>
<td>At 8 weeks: pain NRS sensory score A -10 ± 0.9 vs 4 st control group (con) 98 ± 0.01 FACT-NX summary score A 87 ± 89 vs 4 st control 12 ± 44 P = 0.02. BP SF pain severity score: A -11 ± 1.7 vs 4 st control 0.3 ± 15 P = 0.03</td>
<td>Patient-reported outcomes</td>
<td>No serious adverse effects were observed</td>
</tr>
<tr>
<td>Moassess et al. 53</td>
<td>Randomized, placebo-controlled trial</td>
<td>Varietal</td>
<td>87</td>
<td>At 8 weeks: statistically significant difference detected in pain (primary outcome) in the acn and C-PN20 group and symptoms and functional aspects of quality of life were sustained (P &lt; 0.05). Fourteen weeks improvements in pain interference neurotoxicity-related symptoms and functional aspects of quality of life were sustained (P &lt; 0.05).</td>
<td>Patient-reported outcomes and neurologic assessments</td>
<td></td>
</tr>
<tr>
<td>Investigational Agents/ Authors</td>
<td>Study Design</td>
<td>Neurotoxic Chemotherapy Agent</td>
<td>Evaluable Patients (No.)</td>
<td>Neuropathy Outcomes</td>
<td>Methods</td>
<td>Comments</td>
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<tr>
<td>D’Alessandro et al.</td>
<td>Randomized controlled trial</td>
<td>NR</td>
<td>33</td>
<td>EORTC QLC-C30 statistical differences in physical function (P = 0.03) and sensory symptoms pre-post-treatment (statistically significant better results in acupuncture group (P = 0.03) vs control group which showed no statistical differences after 5 weeks (P = 0.11))</td>
<td>Patient-reported outcomes and cnc neurogic assessments</td>
<td>Intervention included 10 sessions of acupuncture 2 times per week</td>
</tr>
<tr>
<td>Han et al. (acupuncture vs methocobalamin)</td>
<td>Randomized controlled trial</td>
<td>98</td>
<td>VAS pain scores. Met + Acu decreased in 85.7% of patients compared to control group. Decreased in 77.6% of patients. VAS pain scores in the Met + Acu group decreased more significantly compared to the control group (P &lt; 0.01). QOL FACT/GOG-Ntx: significant symptom improvement in the Met + Acu group (P &lt; 0.01) after therapy but not in control group (P &gt; 0.05) and the improvement was more significant in the Met + Acu group (P &lt; 0.05). Nerve conduction velocity after treatment: there was no significant difference between the MOB improvement in the Met + Acu group compared with the control group (P &gt; 0.05).</td>
<td>Patient-reported outcomes and cnc neurogic assessments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rostock et al. (electro-acupuncture)</td>
<td>Randomized controlled trial</td>
<td>Taranis patum der valvetas or vincaroids</td>
<td>60</td>
<td>CPN severity assessed by a 10-point numeric rating scale compared with placebo (1.3 ± 1.3) at acupuncture showed worse effects (0.8 ± 1.2) resulting in a group difference of -0.3 (C 1.4 to 0.8; P = 0.05). No significant differences in sensory nerve conduction studies or quality of life (EORTC QLC-C30) were found</td>
<td>Patient-reported outcomes</td>
<td>Study was stopped early after analysis as no event super or ty of e electro-acupuncture was detected (P &lt; 0.05)</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
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<tr>
<td>Kies et al.</td>
<td>Randomized controlled trial</td>
<td>NR</td>
<td>50</td>
<td>At 12 weeks, the treatment group showed a significant difference in mean pain scores compared to the control group (PPM/PP group). Physical therapy group showed a 70% improvement in the treatment group.</td>
<td>Patient-reported outcomes and cnc neurogic assessments</td>
<td>Intervention included endurance and balance training and strength training. Neurophysiological measures were not the primary outcomes</td>
</tr>
<tr>
<td>Dhawan et al.</td>
<td>Randomized controlled trial</td>
<td>Paclitaxel and carboplatin</td>
<td>45</td>
<td>At 10 weeks, a significant reduction in neuropathic pain scores (P &lt; 0.001) and improvement in QOL (P = 0.0003) and QOL subscores (P = 0.0003) for the treatment group compared to the control group.</td>
<td>Patient-reported outcomes and cnc neurogic assessments</td>
<td>Intervention included home-based muscle strengthening and resistance exercise for 10 weeks</td>
</tr>
</tbody>
</table>

Abbreviations: AE adverse effect, BP Brief Pain Inventory, C-PN chemotherapy-induced peripheral neuropathy, CTCAE Common Terminology Criteria for Adverse Events, EORTC European Organization for Research and Treatment of Cancer FACT-NTX, FACT/GOG-Ntx, Facta oncology Assessment of Cancer Therapy-Neurotoxic Cytotoxic FACT/GOG-Nxt, Facta onco oncology Assessment of Cancer Therapy/Gynecology Oncology Group-Neurotoxic Cytotoxicity, A moderate acupuncture TT, nten to treat MCV, motor conduct on vemics Met + Acu methocobalamin in acupuncture, Met + Acu, methocobalamin, NC Nat ona, Cancer nstute NR not reported, NRS-P Numeric Rating Scale, Pa n, nten to treat, PNQ, Patient Neurotoxic Cytotoxicity, Quest oncana re QOL quality of Life, Quest onna re-Core 30, ST scrambaher therapy, TENS transcutaneous electric nerve stimulation VAS visual analogue scale.
<table>
<thead>
<tr>
<th>Interventions</th>
<th>Strength of Recommendation</th>
<th>Strength of the Evidence</th>
<th>Benefits</th>
<th>Harms*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcysteine</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Acetyl L-carnitine</td>
<td>Strong against</td>
<td>High</td>
<td>No evidence of efficacy</td>
<td>High</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>No recommendation</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Amifostine</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>No evidence of efficacy</td>
<td>Moderate</td>
</tr>
<tr>
<td>Calcium and magnesium</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Cannabinoids</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
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<tr>
<td>Calmangafodipir</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Carbamazepine/oxcarbazepine</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>L-carnosine</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Compression therapy</td>
<td>No recommendation</td>
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<td>Low</td>
<td>Moderate</td>
</tr>
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<td>Cryotherapy</td>
<td>No recommendation</td>
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<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>DDTC</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>No evidence of efficacy</td>
<td>High</td>
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<tr>
<td>Exercise</td>
<td>No recommendation</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Gabapentin/pregabalin</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>GM 1</td>
<td>No recommendation</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Glutamate/glutamine</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>GSH</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>GJJ Kampo medicine</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Metformin</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>No evidence of efficacy</td>
<td>Moderate</td>
</tr>
<tr>
<td>Omega 3</td>
<td>Moderate against</td>
<td>Intermediate</td>
<td>Low</td>
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<td>rhuLIF</td>
<td>Moderate against</td>
<td>Intermediate</td>
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Abbreviations: BAK, topical amitriptyline, ketamine, ± baclofen; DDTC, diethyldithiocarbamate; GJJ, goshajinkigan; GM 1, ganglioside monosialic acid; GSH, glutathione.

*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 neurototoxicity symptoms.21

Calmangafodipir. Calmangafodipir was studied in a placebo-controlled 3-arm phase II trial in patients receiving oxaliplatin-based chemotherapy.26 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/m² 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.98 Two randomized trials investigating GM-1 for CIPN prevention were identified. In the first trial, Zhu et al39 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).48 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.49 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-naïve 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.45

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.46 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 al46 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.43 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 al46 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), it may be that in the Durand et al 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). 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 = 0.07). The small study published subsequently to the meta-analysis 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.

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. 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. 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, including 1 trial that evaluated electro-acupuncture and another that evaluated acupuncture combined with methylcobalamin. 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). 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. 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). 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. 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. 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. One trial randomly assigned patients with CIPN to 3 pharmacotherapy groups: venlafaxine, duloxetine, and placebo. 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). 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 ($P < .001$). 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. 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.

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...
placebo-controlled trial involving 462 patients. Patients established chemotherapy neuropathy in a randomized, Topical amitriptyline/ketamine. A topical 4% amitriptyline/dizziness, and nausea) in the patients receiving the can-ropathy scores between the active and placebo agents. Yet, there was no suggestion of differential benefits in neu-rapathy 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 can-nabinoid 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. 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. 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. 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.

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. 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 gaba-pentin for the treatment of chemotherapy-induced peripheral neuropathy, 2 subsequent trials investigating pregabalin as an agent to prevent chemotherapy-induced neuropathy (1 for paclitaxel 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 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?” 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 dose of this drug can be ≥ 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) 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. 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. 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. 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 ongoing preclinical studies are evaluating the role of neuronal transport, neuroprotection, neuro-inflammation, serotonin-norepinephrine reuptake, nicotinesterase sodium channel inhibition, mitochondrial enzymes, and oxidative stress. 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.

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 (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
REFERENCES


15. Reference deleted.


AUTHOR CONTRIBUTIONS

Conception and design: Charles L. Loprinzi, Christina Lacchetti, Cynthia Chauhan, Mark R. Kelley, Ellen M. Lavoie Smith, Thomas J. Smith, Dawn L. Hersman

Administrative support: Christina Lacchetti

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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.

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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

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

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Research Funding: Bristol Myers Squibb (Inst)
Other Relationship: Hologic/Cynosure

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Guido Cavaletti
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Daniel L. Hertz
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Mark R. Kelley
Leadership: Apelian Pharmaceuticals
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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 Apelian Pharmaceuticals and could eventually receive royalties from Ocupphe Pharma if milestones are met. Ocupphe is an eye company and not cancer related. I have not received any royalties from these units at this time beyond consulting as disclosed. Apelian licensed my IP and then sublicensed IP to Ocupphe for the eye.

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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

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation/Institution</th>
<th>Role/Area of Expertise</th>
</tr>
</thead>
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</tr>
<tr>
<td>(co chair)</td>
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<tr>
<td>Dawn L. Hershman, MD, MS</td>
<td>Columbia University Medical Center, New York, NY</td>
<td>Medical oncology</td>
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<tr>
<td>(co chair)</td>
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<tr>
<td>Maryam B. Lustberg, MD</td>
<td>Ohio State University, Columbus, OH</td>
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<tr>
<td>Thomas J. Smith, MD</td>
<td>Johns Hopkins, Baltimore, MD</td>
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<tr>
<td>Nina Wagner Johnston, MD</td>
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<tr>
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<td>Guido Cavaletti, MD, PhD</td>
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<td>Clinical pharmacology</td>
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<td>Antoinette Lavino, RPh, BCOP</td>
<td>Oncology Pharmacist, PGIN Member, Mass General North Shore</td>
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<tr>
<td>Cancer Center, Danvers, MA</td>
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<tr>
<td>Ellen M. Lavoie Smith, PhD</td>
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<tr>
<td>Cynthia Chauhan, MSW, Patient Advocate</td>
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<td>Patient representative</td>
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<td>Mary Lou Smith, JD, MBA, Patient Advocate</td>
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<tr>
<td>Christina Lacchetti, MHSc</td>
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</tr>
</tbody>
</table>

Abbreviation: PGIN, Practice Guideline Implementation Network.